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(71) Applicant: SRI INTERNATIONAL [US/US]; AA273, 333 Ravenswood Avenue, Menlo Park, CA 94025 (US).

(72) Inventors: DAWSON, Marcia, Ilton ; Post Office Box 1033, Menlo Park, CA 94025 (US). CHAN, Rebecca, Leung-Shun ; 746 Cereza Avenue, Palo Alto, CA 94306 (US). HOBBS, Peter, D. ; 40 Marvin Avenue, Los Altos, CA 94022 (US).

(74) Agents: FAUBION, Urban, H.; Patent Counsel, SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025 (US) et al.

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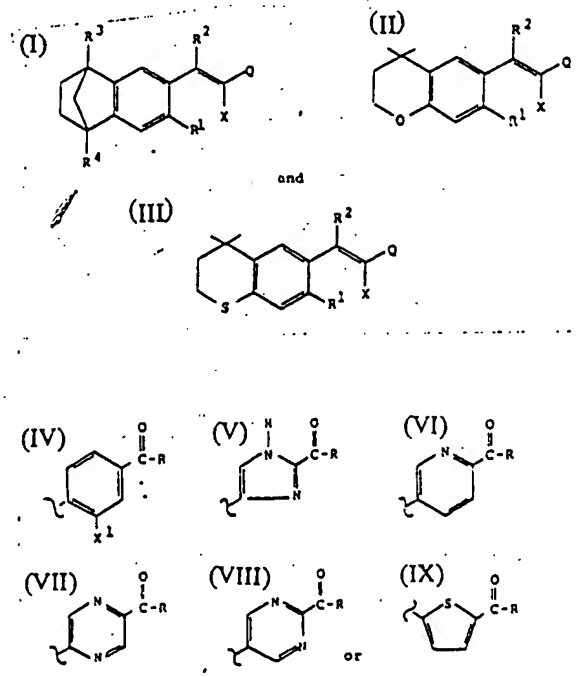
(54) Title: BENZONORBORNENYL, BENZOPYRANYL AND BENZOTHIOPYRANYL RETINOIC ACID ANALOGUES

(57) Abstract

Compounds of the formulas (I), (II) and (III), where R^1, R^2, R^3 and R^4 are hydrogen or methyl, X is hydrogen or fluorine and Q is formula (IV), (V), (VI), (VII), (VIII), or (IX), and X^1 is hydrogen, hydroxy, methoxy or fluorine, R is hydroxy, alkoxy with 0 or 1 hydroxy substituent, aroxy or NR^5R^6, where R^5 is hydrogen, alkyl with 0 or 1 hydroxy substituent or aryl, and R^6 is alkyl with 0 or 1 hydroxy substituent or aryl, with the provisos that X is fluorine only when R^2 is methyl, when R^3 or R^4 is methyl the other R^3 or R^4 is also methyl and when Q is said thienyl group Q may be in either the cis or trans position. These compounds are useful as chemopreventive agents for inhibiting tumor promotion in epithelial cells and for treating nonmalignant skin disorders.



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BENZONORBORNENYL, BENZOPYRANYL AND BENZOTHIOPYRANYL RETINOIC ACID ANALOGUES

Reference to Government Grant or Contract

The invention described herein was made in the course of work under grant from the National Institutes of Health.

Description

Technical Field

The invention is in the fields of retinoid chemistry and chemotherapy. More particularly the invention relates to certain benzonorbornenyl, dihydrobenzopyranyl and dihydrobenzothiopyranyl retinoic acid analogues.

Background Art

The progressive loss of the regulation of cellular differentiation by epithelial cells can result in cancer. Retinoic acid and some of its analogues (retinoids) have been investigated as "chemopreventive" agents, that is, agents that interfere with tumor promotion in epithelial cells. Boutwell, R.K., et al, Advances in Enzyme Regulation V.17, Weber, G., (Ed.), Pergamon Press (1979); Verma, A.K., et al, Cancer Res (1979) 39:419-427; Dawson, M.I., et al, J Med Chem (1980) 23:1013-1022, J Med Chem (1981) 24:583-592, and J Med Chem (1981) 24:1214-1223.

The first Dawson, M.I., et al, articl describes the synthesis of ethyl (E)-3,7-dimethyl-9-(exo-bicyclo[2.2.1]h pt-2- n-2-yl)-2,4,6,8-nonatetraenoate. This compound is highly labile but exhibited activity

in the ornithine decarboxylase (ODC) assay, which assay is described by Verma, A.K. and Boutwell, R.K., Cancer Res (1977) 37:2196-2201. In the latter Dawson article the synthesis of an analogue of the above described norbornenyl retinoid is reported. This compound, ethyl (E)-3,7-dimethyl-9-(exo-2-bicyclo[2.2.1]heptyl)-2,4,6,8-nonatetraenoate, also exhibited activity in the ODC assay.

The second Dawson article, J Med Chem (1981) 24:583-592, describes the preparation of (1E,3E)- and (1Z,3E)-1-(4-carboxyphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene, the methyl and ethyl esters thereof, (E)-1-(2-carboxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene, the methyl ester thereof, (E)-1-[2-(tetrahydropyranyloxy)phenyl]-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene and the (1E,3Z,5E) isomer thereof, and (E)-1-(2-hydroxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene and its (1E,3Z,5E) isomer. Some of these aromatic retinoic acid analogues also exhibited biological activity in the ornithine decarboxylase (ODC) assay.

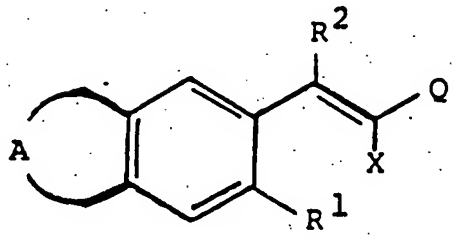
Other reported aromatic retinoic acid analogues with biological activity are 4-[(E)-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-napthyl)-1-propen-1-yl]benzoic acid and ethyl 4-[(E)-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-1-propen-1-yl]benzoate. These compounds exhibit very marked therapeutic ff ct against carcinogen-induced skin papillomas, Loeliger, P., et al, Eur J Med Chem - Chemica Therapeutica (1980) 15:9-15 and West German Patent No. 2,854,354.

A principal object of this invention is to provide r tinoic acid analogu s which are biologically

active and which may exhibit lesser toxicity than other retinoic acid analogues.

Disclosure of the Invention

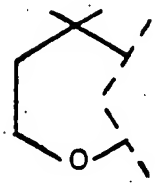
The retinoic acid analogues of the invention are compounds of the formula:



(1)

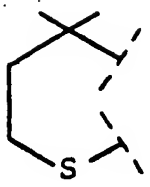
where A is the substituent system of a fused ring selected from:

(a)



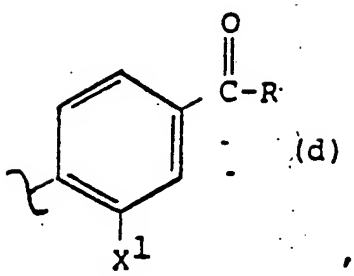
(b)

or



(c)

and R^1, R^2, R^3 and R^4 are hydrogen or methyl, X is hydrogen or fluorine and Q is: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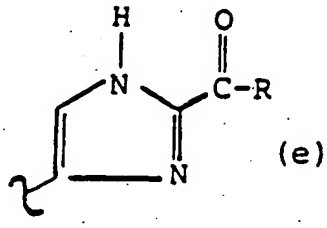
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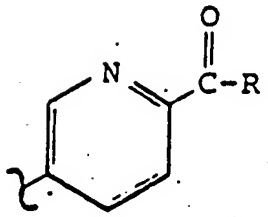
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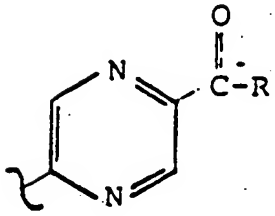
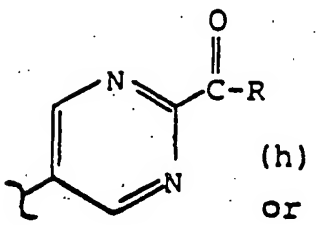
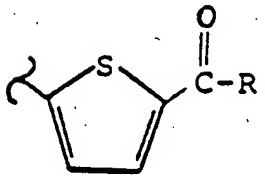

(g)


(h)

or


(i)

where X^1 is hydrogen, hydroxy, methoxy or fluorine, R is hydroxy, alkoxy with 0 or 1 hydroxy substituent, aroxy or NR^5R^6, where R^5 is hydrogen, alkyl with 0 or 1 hydroxy substituent or aryl and R^6 is alkyl with 0 or 1 hydroxy substituent or aryl, with the provisos that X is fluorine only when R^2 is methyl, when R^3 or R^4 is methyl, the other R^3 or R^4 is also methyl, and when Q is (i) Q may be in either the <u>cis</u> or <u>trans</u> position.

When us d as pharmaceuticals, eg, as a chemopreventive agent or for treating skin disorders such as prolif rative skin dis ases or acne, one or mor of these retinoids is combined with a suitable pharmaceutically acc ptable carrier and an effectiv dose th reof is administ red to the patient.

Modes for Carrying Out the Invention

The alkoxy groups represented by R will usually contain 1 to about 10 carbon atoms and have 0 or 1 hydroxy substituent. They will preferably contain 1 to 4 carbon atoms, and have 0 or 1 hydroxy substituent. The alkoxy groups represented by R may be straight chain or branched chain. Examples of such alkoxy groups are methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, n-hexoxy, 2-methylpentoxy, n-heptoxy, 2-hydroxyethoxy, 3-methylhexoxy, n-octoxy, and n-decoxy. The aroxy groups represented by R will usually be mononuclear and contain 6 to 15 carbon atoms, more usually 6 to 10 carbon atoms and have 0 or 1 hydroxy or C_1-C_4 alkoxy substituent. Preferred aroxy groups are phenoxy and hydroxy- or C_1-C_4 alkoxy-monosubstituted phenoxy. Examples of aroxy groups are phenoxy, o-, m-, or p-hydroxyphenoxy, o-, m-, or p-methoxyphenoxy, toloxy, cumoxy, xyloxy, and naphthoxy.

The alkyl groups represented by R^1 and R^2 may be straight chain or branched chain. They will typically each contain 1 to 8 carbon atoms with 0 or 1 hydroxy substituent, preferably 1 to 4 carbon atoms, and have 0 or 1 hydroxy substituent. Examples of such alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, n-amyl, n-hexyl, 2-methylamyl, n-heptyl, 3-methylhexyl, n-octyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxyhexyl, and the like. The corresponding aryl groups represented by R^1 and R^2 may be substituted or unsubstituted mononuclear or polynuclear moieties. The substituents will usually be lower (ie, 1 to 4 carbon atoms) alkyl, monohydroxyalkyl, lower alkoxy, monohydroxyalkoxy or hydroxy. When substituted, the group will usually be

mono-substituted. Examples of such groups are phenyl, o-, m-, or p-hydroxyphenyl, o-, m-, or p-methoxyphenyl, ethylbenzyl, cumyl, and the like. These aryl groups will usually contain 6 to about 15 carbon atoms, more usually 6 to 10 carbon atoms. Phenyl, 4-hydroxyphenyl, and 4-methoxyphenyl are preferred aryl groups.

Examples of acids (R = OH) are:

(E)-1-(4-carboxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-fluorophenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-methoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-pyridyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-4-imidazolyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-pyrazinyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-pyrimidinyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-thienyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(Z)-1-(2-carboxy-5-thienyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxyphenyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-fluorophenyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-methoxyphenyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(2-carboxy-5-pyridyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(2-carboxy-4-imidazolyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(2-carboxy-5-pyrazinyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(2-carboxy-5-pyrimidinyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(2-carboxy-5-thienyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(Z)-1-(2-carboxy-5-thienyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxyphenyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-fluorophenyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-methoxyphenyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxyphenyl)-1-fluoro-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-fluorophenyl)-1-fluoro-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-hydroxyphenyl)-1-fluoro-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-methoxyph nyl)-1-fluoro-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxyph nyl)-1-fluoro-2-(1,4-methano-7-m thyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propen
(E)-1-(4-carboxy-2-fluorophenyl)-1-fluoro-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-

(E)-1-(4-carboxy-2-hydroxyphenyl)-1-fluoro-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-methoxyphenyl)-1-fluoro-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-thienyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(Z)-1-(2-carboxy-5-thienyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-thienyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(Z)-1-(2-carboxy-5-thienyl)-2-(1,4-methano-7-methyl-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxyphenyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-fluorophenyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(4-carboxy-2-methoxyphenyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-pyridyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-4-imidazolyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-pyrazinyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-pyrimidinyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(E)-1-(2-carboxy-5-thienyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

(Z)-1-(2-carboxy-5-thienyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propen

(E)-1-(4-carboxyphenyl)-1-fluoro-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-fluorophenyl)-1-fluoro-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-hydroxyphenyl)-1-fluoro-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-methoxyphenyl)-1-fluoro-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxyphenyl)-1-fluoro-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-fluorophenyl)-1-fluoro-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(Z)-1-(2-carboxy-5-thienyl)-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-hydroxyphenyl)-1-fluoro-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
(E)-1-(4-carboxy-2-methoxyphenyl)-1-fluoro-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene
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(E)-1-(2-carboxy-5-pyridyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene

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(E)-1-(4-carboxy-2-fluorophenyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxy-2-methoxyphenyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(2-carboxy-5-pyridyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(2-carboxy-4-imidazolyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-t trahydro-6-naphthyl) thene
(E)-1-(2-carboxy-5-pyrazinyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-t trahydro-6-naphthyl)ethene
(E)-1-(2-carboxy-5-pyrimidinyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene

(E)-1-(2-carboxy-5-thienyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(Z)-1-(2-carboxy-5-thienyl)-2-(1,4-dimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(Z)-1-(2-carboxy-5-thienyl)-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(2-carboxy-5-thienyl)-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxy-2-fluorophenyl)-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxy-2-methoxyphenyl)-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxyphenyl)-1-fluoro-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxy-2-fluorophenyl)-1-fluoro-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxy-2-hydroxyphenyl)-1-fluoro-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxy-2-methoxyphenyl)-1-fluoro-2-(1,4,7-trimethyl-1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene
(E)-1-(4-carboxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-5-pyridyl)-2-(4,4-dimethyl-2,3-dihydro-1-b nzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-4-imidazolyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-5-pyrazinyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene

(E)-1-(2-carboxy-5-pyrimidinyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-5-thienyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(4-carboxyphenyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-5-pyridyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-4-imidazolyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-5-pyrazinyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-5-pyrimidinyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(2-carboxy-5-thienyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(4-carboxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(E)-1-(2-carboxy-5-pyridyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(E)-1-(2-carboxy-4-imidazolyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(E)-1-(2-carboxy-5-pyrazinyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(E)-1-(2-carboxy-5-pyrimidinyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(Z)-1-(2-carboxy-5-thienyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(E)-1-(4-carboxyph nyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl) thene
(E)-1-(2-carboxy-5-pyridyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-propene
(E)-1-(2-carboxy-4-imidazolyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-propene

(E)-1-(2-carboxy-5-pyrazinyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-propene
(E)-1-(2-carboxy-5-pyrimidinyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-propene
(Z)-1-(2-carboxy-5-thienyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-propene
(E)-1-(4-carboxy-2-fluorophenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-fluorophenyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-fluorophenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)ethene
(E)-1-(4-carboxy-2-fluorophenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(E)-1-(4-carboxy-2-fluorophenyl)-1-fluoro-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-fluorophenyl)-1-fluoro-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-methoxyphenyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-methoxyphenyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-methoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(E)-1-(4-carboxy-2-methoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)ethene
(E)-1-(4-carboxy-2-methoxyphenyl)-1-fluoro-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-methoxyphenyl)-1-fluoro-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(4,4,7-trimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propen
(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-b nzopyran-6-yl)-1-propene

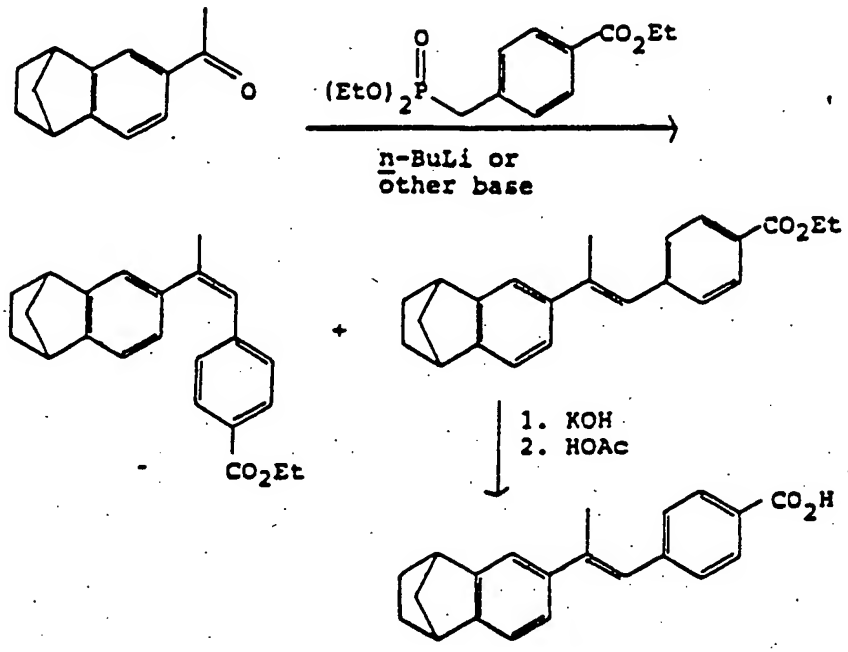
(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)ethene
(E)-1-(4-carboxy-2-hydroxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)ethene
(E)-1-(4-carboxy-2-hydroxyphenyl)-1-fluoro-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene
(E)-1-(4-carboxy-2-hydroxyphenyl)-1-fluoro-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene

Examples of esters (R = alkoxy, aroxy) are the methyl, ethyl, isopropyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, hydroxymethyl, 2-hydroxyethyl, 3 hydroxypropyl, phenyl, p-hydroxyphenyl, o-hydroxyphenyl, p-methoxyphenyl, tolyl, and naphthyl esters of the above acids.

Examples of carboxamides (R = NR^5R^6) are the N-methyl, N-isopropyl, N-hexyl, N-octyl, N-2-hydroxyethyl, N-3-hydroxypropyl, N,N-dimethyl, N-phenyl, N-p-hydroxyphenyl, N-p-methoxyphenyl, and N-p-ethoxyphenyl carboxamides of the above acids and esters.

The retinoids of formula (1) where X, X_1, R^1, R^3 and R^4 are hydrogen, R^2 is methyl, the fused ring group is a benzonorbornene and Q is carboxyphenyl

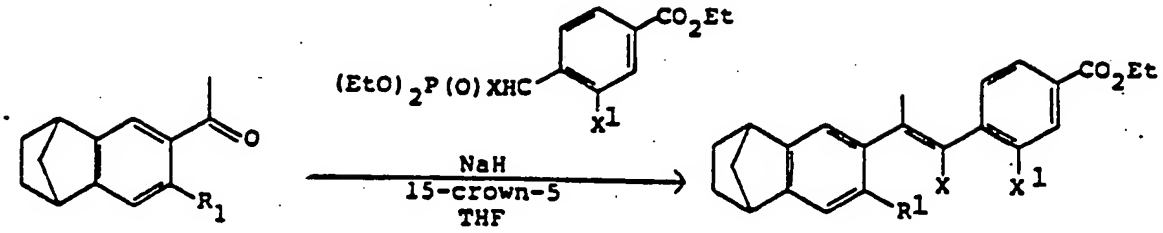
or carbethoxyphenyl may be made by the following route:



Ac = $H_3CC(O)$-

Other esters and esters of the other aromatics may be made by starting with the desired phosphonate of the appropriate aromatic carboxyl ester. The carboxamides may be made from the acids by conversion to acid chlorides or activated esters followed by reaction with an appropriate amine.

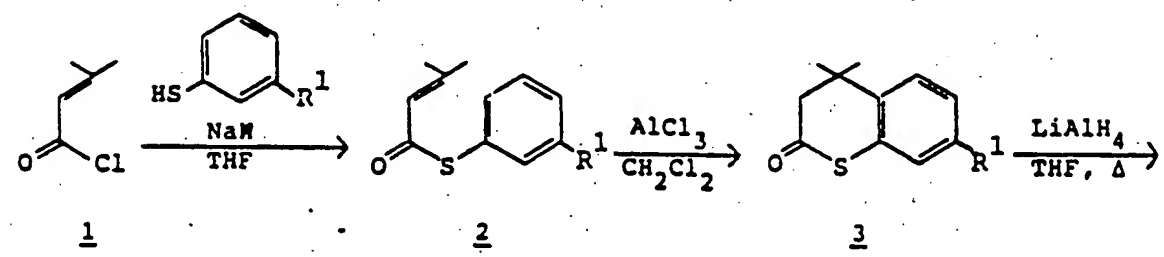
The preparation of the fluoro, methyl, methoxy and hydroxy substituted benzonorbornenyl retinoids may also be achieved using this same type of synthesis schem :

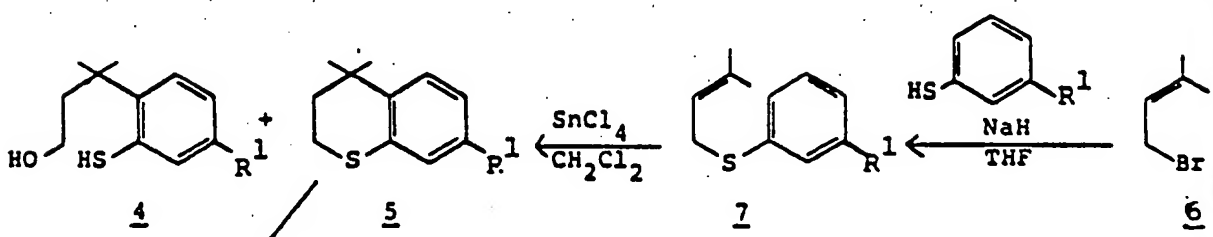


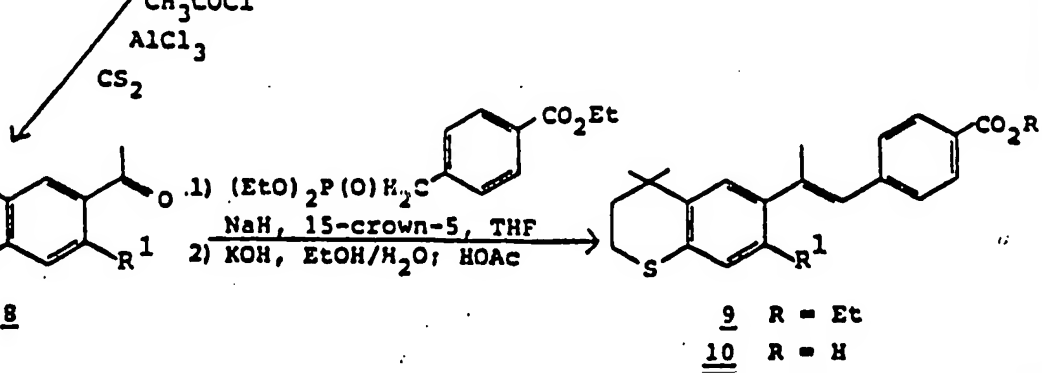
where R = H or Me
X^1 = H or F
X^1 = F, OMe or OH

15-crown-5 = 1,4,7,10,13-pentaoxacyclopentadecane and THF = tetrahydrofuran.

The dihydrobenzothiopyranyl retinoids of formula 1 may be made by the following schemes:

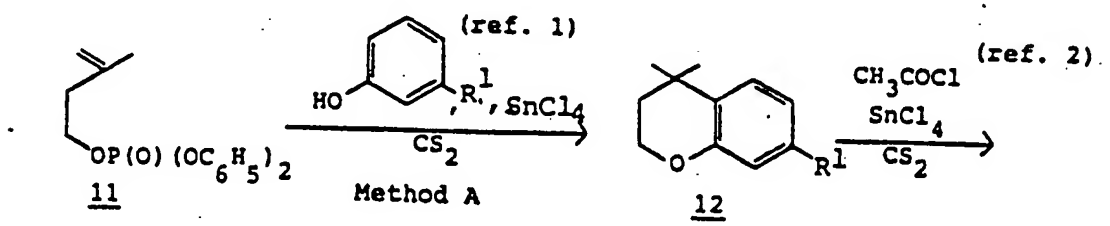


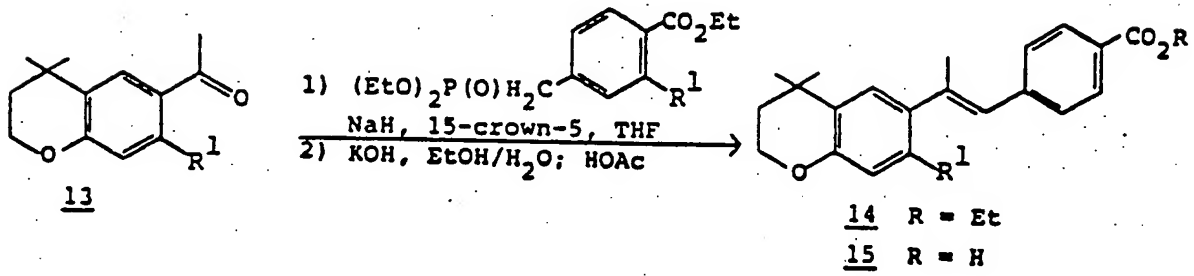




Ac = $H_3CC(O)$-, THF = tetrahydrofuran, and 15-crown-5 = 1,4,7,10,13-pentaoxacyclopentadecane.

According to the following method the dihydrobenzopyrans are made analogously from the oxygen analog of 2,3-dihydro-4,4-dimethyl-1-benzothiopyran (compound 5 in the above scheme):

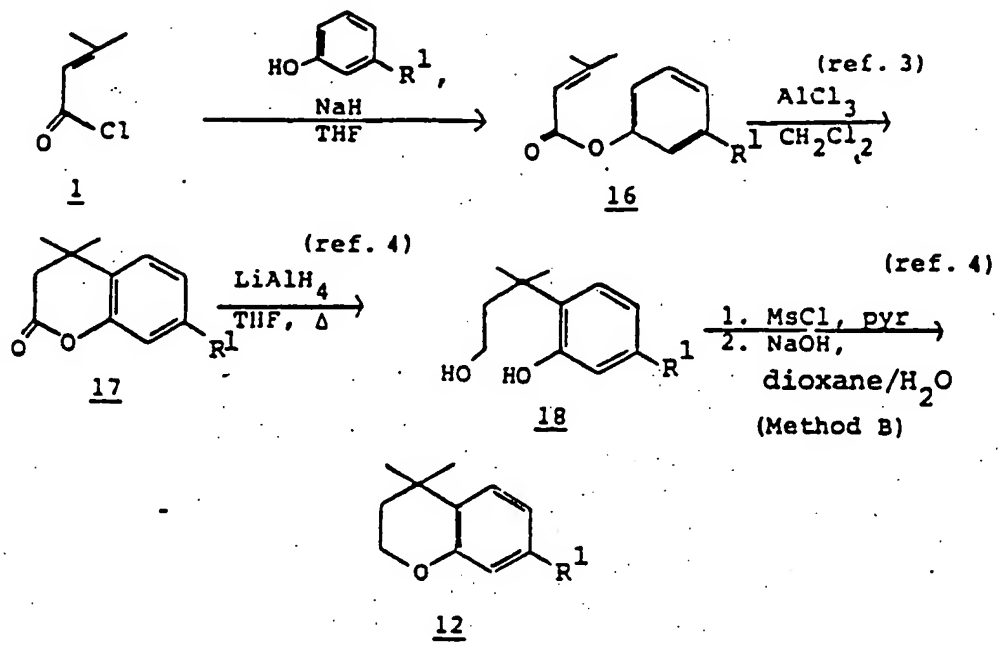




Where the abbreviations are as above.

An alternative method (Method B) for preparing 2,3-dihydro-4,4-dimethyl-1-benzopyran (compound 12 in the above scheme) is as follows:

(1) Butsugan, Y., t al, Chem Lett (1976) 523.
(2) Chatelus, G., Ann Chim (1949) 4:505.



1 16 17 18 12

As in the case of the benzonorborene compounds other esters and esters of other aromatics of the benzopyran and benzothiopyran compounds may be made by varying the phosphonate reactant.

The following examples further illustrate the invention compounds and their preparation. These examples are not intended to limit the invention in any manner. Abbreviations used in the examples are Me = methyl, Et = ethyl, Bu = butyl. NBS = N-bromo-succinimide, Ac = $H_3CC(O)$-, LDA = lithio diisopropyl-amide, THF = tetrahydrofuran, LC = high-performance liquid chromatography, IR = infrared, NMR = nuclear magnetic resonance, UV = ultraviolet, DMF = dimethyl-formamide, GC = gas chromatography, TLC = thin layer

(3) Milstien, S., t al, J Amer Chem Soc (1972) 94:9158.
(4) Borchardt, R.T., et al, J Amer Chem Soc (1972) 94:9166.

chromatography, Pd/C = palladium on carbon, and 15-crown-5 = 1,4,7,10,13-pentaoxacyclopentadecane.

Example 1. Preparation of (E)-1-(4-Carboethoxyphenyl)-2-(1,4 methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene and (E)-1-(4-Carboxyphenyl)-2-(1,4 methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene

1,4-Methano-1,4-dihydronaphthalene. Cyclopentadiene (bp 39-40°C) was prepared by heating the dimer and distilling twice through a 10-cm Vigreaux column packed with glass helices. It was stored at -78°C before use. To 4.0 g (0.166 mol) of powdered Mg (20 to 100 mesh) was added 10 mL of a solution of 26 g (0.15 mol) of o-fluorobromobenzene and 9.8 g (0.15 mol) of cyclopentadiene in 90 mL of THF. The reaction started instantaneously. The remaining solution was added dropwise over a period of 45 min to maintain a gentle reflux. When the addition was complete, the mixture was stirred for another 45 min at room temperature. It was then diluted with 50 mL of THF and filtered. The filtrate was concentrated to a small volume and about 150 mL of saturated NH_4Cl was added. The product was extracted with Et_2O (3 x 100 mL). The Et_2O layer was dried (Na_2SO_4) and evaporated to give 16 g of a yellow oil. This oil was distilled at 50-54°C (1.75 mm) to give 10.7 g of the product, which was still contaminated with some polar impuriti s by TLC. The distillate was passed over 200 g of SiO_2 (5% Et_2O/hexane) to give 10.2 g of product as a yellow oil (48% yield): IR (film) 3080, 3000, 2950, 2890, 1460, 1310, 1240, 1020, 840, 760, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 2, CH_2), 3.83

(m, 2, CH), 6.8-7.4 (m, 6, HC=CH, ArH); MS calculated for $C_{11}H_{10}$ 142.0782, found 142.0781.

1,4-Methano-1,2,3,4-tetrahydronaphthalene. To 16.0 g (0.113 mol) of the purified 1,4-methano-1,4-dihydronaphthalene in 150 mL of absolute EtOH was added 1.0 g of 5% Pd/C. This mixture was hydrogenated at room temperature and atmospheric pressure. After about 20 h, TLC indicated that no starting material remained. The reaction mixture was filtered, concentrated and distilled to afford 10.0 g (62% yield) of the product as a colorless oil: bp 67°C (4.5 mm): IR (film) 3070, 3030, 2980, 2880, 1490, 1470, 1320, 1300, 1260, 1160, 1120, 1080, 1020, 960, 940, 880, 840, 760, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1-1.5 (m, 2, $HCCH_2CH$), 1.5-2.1 (m, 4, $(CH_2)_2$), 3.35-3.5 (m, 2, CH), 7.0-7.3 (m, 4, ArH); MS calcd for $C_{11}H_{12}$ 144.0939, found 144.0930.

6-Acetyl-1,4-methano-1,2,3,4-tetrahydronaphthalene. A mixture of 6.9 g (47.9 mmol) of 1,4-methano-1,2,3,4-tetrahydronaphthalene and 4.14 g (52.7 mmol) of AcCl was added dropwise over a period of 20 min to a stirred suspension of 7.34 g (55 mmol) of $AlCl_3$ in 50 mL of $ClCH_2CH_2Cl$, which was cooled in a water bath at 20°C. When the addition was complete, the mixture was stirred at room temperature for 1 h. The reaction was quenched with 100 mL of ice-water and extracted with Et_2O (2 x 150 mL). The Et_2O layer was dried and concentrated to give 10.6 g of a yellow oil. Distillation gave 8.1 g (91% yield) of the product as a pal yellow oil, bp 102°C (0.2 mm): IR (film) 3000, 2900, 1690, 1630, 1590, 1440, 1370, 1310, 1280, 1200, 1160, 1120, 1030, 960, 920, 850, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05-1.3 (m, 2, $CHCH_2CH$), 1.4-2.1 (m, 4, $(CH_2)_2$), 2.57

(s, 3, CH_3CO), 3.3-3.5 (m, 2, CH), 7.27 (d, J = 8 Hz, 1, 8-ArH), 7.77 (dd, J = 2 Hz, J = 8 Hz, 1, 7-ArH), 7.83 (d, J = 2 Hz, 1, 5-ArH); MS calcd for $C_{13}H_{14}O$ 186.1045, found 186.1036.

(E)-1-(4-Carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene and (Z)-1-(4-Carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene. Diethyl 4-carbethoxybenzylphosphonate was prepared in 76% yield.(5) A solution of 13.8 g (46 mmol) of this phosphonate in 150 mL of THF was cooled to -20°C, while 30 mL (45.6 mmol) of a 1.52 M solution of n-BuLi in hexane was added over a period of 15 min. The dark brown solution was warmed up to 0°C and 8.6 g (46.2 mmol) of 6-acetyl-1,4-methano-1,2,3,4-tetrahydronaphthalene in 10 mL of THF was added. The mixture was stirred at room temperature for 16 h. The reaction mixture was next poured onto 500 mL of ice-water and extracted with Et_2O (3 x 200 mL). The Et_2O layer was dried (Na_2SO_4) and concentrated to give about 20 g of a yellow oil. This oil was partially purified on 150 g of silica gel (7% Et_2O/hexane) to give 3.0 g of the unreacted starting material, 6-acetyl-1,4-methano-1,2,3,4-tetrahydronaphthalene, and 7.0 g (70% yield from the amount of ketone consumed) of an approximately 2:1 mixture of Z and E isomers, (Z)-1-(4-carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene and (E)-1-(4-carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene, respectively. A purification of the mixture by LC (1% Et_2O/hexane)

(5) Kreutzkamp, N. and Cordes, G., Arch Pharm

gave 3.0 g of a mixture containing over 90% of the Z isomer and 3.5 g of a 1:1 mixture of Z and E isomers. A solution of 3.0 g of the 9:1 Z/E mixture in 500 mL of CH_2Cl_2 was irradiated with a medium-pressure Hanovia Hg-arc lamp for 5 h to give a 1:1 mixture of the Z and E isomers. The combined mixtures were purified by multiple passes on LC (1% Et_2O/hexane) to give 2.0 g (20%) of the E isomer (E)-1-(4-carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene and 2.1 g (21%) of the Z isomer, (Z)-1-(4-carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene. E-isomer: LC (Radialpak B, 2% Et_2O/hexane, 3 mL/min, 260 nm) t_R 5.0 min (0.5%), 5.7 min (99.5%); LC (Radialpak A, 5% H_2O/MeCN, 2 mL/min, 260 nm) t_R 6.2 min (100%); IR (film) 3000, 2900, 1730, 1620, 1580, 1490, 1460, 1420, 1380, 1290, 1190, 1110, 1030, 960, 890, 830, 770, 750, 710 cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$) δ 1.15-2.30, 1.50-1.60, and 1.90-2.00 (3 m, 6, $(CH_2)_2$, $HCC\underline{H}_2CH$), 1.41 (t, J = 7 Hz, 3, $CH_2\underline{CH}_3$), 2.29 (s, 3, CH_3), 3.37 (s, 2, CH), 4.38 (q, J = 7 Hz, 2, $CO_2\underline{CH}_2CH_3$), 6.81 (s, 1, C=CH), 7.16 (d, J = 8 Hz, 1, 8-ArH), 7.24 (d, J = 8 Hz, 1, 7-ArH), 7.35 (s, 1, 5-ArH), 7.40 (d, J = 8Hz, 2, 2',6'-H), 8.03 (d, J = 8 Hz, 2, 3',5'-H); ^{13}C NMR ($CDCl_3$) 14.3 ($CH_2\underline{CH}_3$), 17.8 ($C=C\underline{CH}_3$), 27.0 ($(\underline{CH}_2)_2$), 43.4 ($HC\underline{CH}_2CH$), 43.8, 49.2 (CH), 60.7 ($\underline{CH}_2CH_3$), 118.2, 120.2, 123.3, 125.8, 128.0, 128.9 and 129.3 (C-2',3',5',6'), 140.1, 141.0, 143.3, 147.8, 148.3, 166.4 ppm (CO_2); UV (EtOH) λ_{max} 308 nm (ε 2.66 x 10^4), 233 nm (ε 1.49 x 10^4), 206 nm (ε 2.68 x 10^4); MS calcd for $C_{23}H_{24}O_2$ 332.1776, found 332.1757. Z-isomer: LC (Radialpak B, 2% Et_2O/hexane, 3 mL/min, 260 nm) t_R 5.0 min (99%), 5.7 min (1%); LC (Radialpak A, 5% H_2O/MeCN, 2 mL/min, 260 nm) t_R 5.9 min (100%); IR (film) 3000,

2900, 1730, 1620, 1580, 1490, 1460, 1420, 1380, 1290, 1190, 1110, 1030, 960, 890, 830, 770, 750, 710 cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$) δ 1.10-1.20, 1.45-1.55 and 1.80-1.90 (3 m, 6, $(CH_2)_2$, $HCC\underline{H}_2CH$), 1.35 (t, J = 7 Hz, 3, $CH_2C\underline{H}_3$), 2.21 (s, 3, $C{=}CCH_3$), 3.25 and 3.34 (2 s, 2, CH), 4.34 (q, J = 7 Hz, 2, $C\underline{H}_2CH_3$), 6.42 (s, 1, C=CH), 6.85 (d, J = 8 Hz, 1, 7-ArH), 6.94 (s, 1, 5-ArH), 6.95 (d, J = 8 Hz, 2, 2',6'-H), 7.06 (d, J = 8 Hz, 1, 8-ArH), 7.73 (d, J = 8 Hz, 2, 3',5'-H); ^{13}C NMR ($CDCl_3$) 14.3 ($CH_2\underline{C}H_3$), 27.1 ($(CH_2)_2$), 27.5 ($C{=}C\underline{C}H_3$), 43.5 ($HC\underline{C}H_2CH$), 43.7 and 49.1 (CH), 60.6 ($\underline{C}H_2CH_3$), 120.1, 120.5, 124.9, 125.2, 127.6, 128.6 and 128.9 (2',3',5',6'), 138.7, 142.5, 142.7, 147.4, 148.5, 166.5 ppm (CO_2); UV (EtOH) λ_{max} 300 nm (ε 1.68 x 10^4), 239 nm (ε 1.67 x 10^4), 205 nm (ε 2.89 x 10^4); MS calcd for for $C_{23}H_{24}O_2$ 332.1776, found 332.1741.

(Z)-1-(4-Carboxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene. To a solution of 1.8 g (5.42 mmol) of the Z-ester in 20 mL of warm EtOH was added a solution of 1.5 g of KOH (26.7 mmol) in 2 mL of H_2O and 3 mL of EtOH. The mixture was degassed three times under argon and heated in an 80°C oil bath for 30 min. The cooled solution was acidified with 20 mL of 50% H_2O/HOAc. The precipitated acid was extracted into 100 mL of Et_2O. The Et_2O layer was washed with 100 mL of brine, dried ($MgSO_4$), and evaporated. The crude acid was recrystallized from MeOH to give 1.3 g (79% yield) of (Z)-1-(4-carboxyphenyl)-2-(1,4 methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene as white crystals, mp 188°C: LC (Radialpak A, reverse phase, 40% H_2O/CH_3CN, 2 mL/min, 260 nm) t_R 1.3 min (100%); IR (mull) 1690, 1610, 1320, 1300, 1180, 1120, 940, 880, 830, 770, 730, 700 cm^{-1};

300 MHz ^{1}H NMR ($CDCl_3$) δ 1.10-1.30, 1.45-1.55 and 1.80-1.95 (3 m, 6, $(CH_2)_2$, $HCC\underline{H}_2CH$), 2.23 (s, 3, CH_3), 3.25 and 3.34 (2 s, 2, CH), 6.44 (s, 1, C=CH), 6.86 (d, J = 8 Hz, 1, 7-ArH), 6.94 (s, 1, 5-ArH), 6.97 (d, J = 8 Hz, 2, 2',6'-H), 7.08 (d, J = 8 Hz, 1, 8-ArH), 7.77 (d, J = 8 Hz, 2, 3',5'-H) 9.5-10.4 (broad s, 1, CO_2H); ^{13}C NMR ($CDCl_3/Me_2SO-d_6$) 26.9 ($(CH_2)_2$), 27.2 ($C=C\underline{C}H_3$), 43.3 ($HC\underline{C}H_2CH$), 43.4 and 48.9 (CH), 119.9, 120.3, 124.7, 125.0, 127.3, 128.5 and 129.1 (2',3',5',6'), 138.4, 142.3, 142.7, 147.2, 148.3, 169.4 ppm (CO_2); UV (EtOH) λ_{max} 293 nm (ε 1.43 x 10^4), 280 nm (ε 1.39 x 10^4), 238 nm (ε 1.44 x 10^4); MS calcd for $C_{21}H_{20}O_2$ 304.1463, found 304.1436.

(E)-1-(4-Carboxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene. A solution of 1.5 g (26.7 mmol) of KOH in 2 mL of H_2O and 3 mL of EtOH was added to a warm solution of 2.0 g (6.02 mol) of (E)-1-(4-carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene in 20 mL of EtOH. The mixture was degassed under argon three times and then heated at 80°C for 30 min, cooled and acidified with 20 mL of 50% H_2O/HOAc. The acid was extracted with 100 mL of Et_2O. The Et_2O solution was washed with 100 mL of brine, dried ($MgSO_4$), and concentrated to give 1.8 g of the crude acid, which was recrystallized from EtOAc to afford 1.2 g (66% yield) of white crystals, mp 209°C: LC (Radialpak A, 40% H_2O/MeCN, 2 mL/min, 260 nm) t_R 1.25 min (100%); IR (mull) 1690, 1610, 1320, 1300, 1180, 1120, 960, 890, 830, 720 cm^{-1}; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.20-1.30, 1.50-1.60 and 1.85-1.95 (3 m, 6, $(CH_2)_2$, $HCC\underline{H}_2CH$), 2.31 (s, 3, CH_3), 3.39 (s, 2, CH), 6.82 (s, 1, C=CH), 7.16 (d, J = 8 Hz, 1, 8-ArH), 7.25 (d, J = 8 Hz, 1, 7-ArH), 7.36 (s, 1,

5-ArH), 7.45 (d, J = 8 Hz, 2, 2',6'-H), 8.08 (d, J = 8 Hz, 2, 3',5'-H), 8.4-9.0 (broad s, 1, CO_2H); ^{13}C NMR ($CDCl_3/Me_2SO-d_6$) 17.7 (CH_3), 26.8 ($(CH_2)_2$), 43.2 ($HC\underline{C}H_2CH$), 43.6 and 49.0 (CH), 118.0, 120.0, 123.1, 125.7, 128.7 and 129.4 (2',3',5',6'), 139.8, 140.8, 142.9, 147.6, 148.2, 168.4 ppm (CO_2); UV (EtOH) λ_{max} 301 nm (ε 2.45 x 10^4), 227 nm (ε 1.35 x 10^4); MS calcd for $C_{21}H_{20}O_2$ 304.1463, found 304.1451.

Example 2. Preparation of (E)-1-(4-Carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene and (E)-1-(4-Carboxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene.

Phenyl 3,3-Dimethylthiolacrylate. To a degassed (argon) suspension of NaH, which was obtained from 3.2 g (80 mmol) of 60% NaH/mineral oil dispersion, which had been washed with hexane (3 x 15 mL) under argon, in 30 mL of THF, was added over a period of 5 min with stirring and cooling in ice a solution of 8.8 g (80 mmol) of thiophenol in 80 mL of THF. The suspension was stirred for a further 15 min and then treated with a solution of 10.1 g (85 mmol) of 3,3-dimethylacryloyl chloride in 40 mL of THF over a period of 10 min and then allowed to warm to room temperature over a 2-h period. The suspension was poured into 200 mL of water containing 2 mL of HOAc and stirred for 15 min and then extracted with 200 mL of Et_2O. The extract was washed with dilute brine (3 x 100 mL), dried (Na_2SO_4), and concentrated to give a yellow oil. Distillation yielded the thiolester, phenyl 3,3-dimethylthiolacrylate, as 15.0 g (98% yield) of colorless liquid, bp 105-106°C (0.7 mm); IR ($CHCl_3$) 1680, 1625, 1475 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88,

2.14 (2 s, 6, $(CH_3)_2C$), 6.07 (m, 1, C=CH), 7.43 (m, 5, ArH); MS calcd for $C_{11}H_{12}OS$ 192.061, found 192.059.

2,3-Dihydro-4,4-dimethyl-2-oxo-1-benzothiopyran. A stirred, ice-cooled suspension of 14.0 g (105 mmol) of $AlCl_3$ in 100 mL of CH_2Cl_2 was treated with a solution of 13.44 g (70 mmol) of phenyl 3,3-dimethylthiolacrylate in 70 mL of CH_2Cl_2. The reaction mixture was allowed to stand at 0°C for 15 h and then was poured onto 200 g of ice/brine. The aqueous phase was extracted with 100 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with dilute brine (2 x 150 mL) and water (150 mL), dried (Na_2SO_4), and concentrated. The pale yellow liquid (13.5 g) was chromatographed on a 7 x 35-cm column of silica gel (10% Et_2O/hexane) to give 12.24 g (91% yield) of the thiolactone, 2,3-dihydro-4,4-dimethyl-2-oxo-1-benzothiopyran, as a solid, mp 34-35°C; IR ($CHCl_3$) 1680, 1595, 1475 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 6, $(CH_3)_2C$), 2.65 (s, 2, CH_2CO), 7.15-7.63 (m, 4, ArH); MS calcd for $C_{11}H_{12}OS$ 192.061, found 192.059.

2,3-Dihydro-4,4-dimethyl-1-benzothiopyran. Method A. To 1.0 g (26 mmol) of $LiAlH_4$, which was stirred under argon in an ice bath, was added 15 mL of THF. This suspension was degassed twice with argon. A solution of 0.96 g (5.0 mmol) of 2,3-dihydro-4,4-dimethyl-2-oxo-1-benzothiopyran in 6 mL of THF was introduced dropwise at room temperature. The reaction mixture was then refluxed for 4 h, cooled in ice/water, and the excess $LiAlH_4$ was quenched by the dropwise addition of 20% EtOAc/THF. The mixture was poured onto 50 mL of 2 N H_2SO_4 and extracted with 2 x 25 mL of Et_2O. The extract was washed with

diluted brine (3 x 25 mL), dried (Na_2SO_4), and concentrated. The colorless oil (0.95 g) was chromatographed on a 2 x 30-cm silica gel column, which was eluted with 350 mL of 2% Et_2O/hexane, to give, successively, (a) 0.36 g (40% yield) of 2,3-dihydro-4,4-dimethyl-1-benzothiopyran, as a colorless liquid: IR ($CHCl_3$) 1595, 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 6, $(CH_3)_2C$), 1.90 (m, 2, CCH_2), 2.98 (m, 2, CH_2S), 6.87 (m, 3, ArH), 7.27 (m, 1, ArH); MS calcd for $C_{11}H_{14}S$ 178.081, found 178.080; and (b) 0.51 g (52% yield) of the alcohol (compound 4 on page 15) as a colorless gum: IR ($CHCl_3$) 3600, 3430, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 6, $(CH_3)_2C$), 2.12 (broad s, 1, OH, exchanged D_2O), 2.23 (t, J = 8 Hz, 2, CCH_2), 3.38 (t, J = 8 Hz, 2, CH_2O), 3.60 (broad s, 1, SH, exchanged D_2O), 6.90-7.38 (m, 4, ArH); MS calcd for $C_{11}H_{16}OS$ 196.092, found 196.089.

Method B: To a solution of 22.9 g (88 mmol) of $SnCl_4$ in 200 mL of CH_2Cl_2, cooled in ice, was added a solution of 7.83 g (44 mmol) of 3-methyl-2-buten-1-yl phenyl sulfide in 40 mL of CH_2Cl_2. The solution was stirred at 0-5°C for 20 min and then at room temperature for 20 h. The red solution was poured onto 500 g of ice/brine, and the organic extract was washed successively with 250-mL volumes of brine, aqueous $NaHCO_3$, and water (three times). The CH_2Cl_2 solution, which contained suspended inorganic material, was dried (Na_2SO_4), filtered, and concentrated. The 7.4 g of yellow liquid was chromatographed twice using a 4.5 x 40-cm silica gel column with 0.75% Et_2O/hexane to give 4.11 g (52% yield) of 2,3-dihydro-4,4-dimethyl-1-benzothiopyran, a colorless liquid. The product was spectrally (IR, NMR) id ntical with the sample pr par d by the $LiAlH_4$ reduction of 2,3-dihydro-4,4-dimethyl-2-oxo-1-benzothiopyran.

3-Methyl-2-buten-1-yl Phenyl Sulfide. A stirred suspension of NaH, which was obtained by washing (hexane, 3 x 15 mL) 3.0 g (75 mmol) of 60% NaH/mineral oil dispersion under argon, in 20 mL of THF was cooled under argon in ice/water and treated with 7.15 g (65 mmol) of thiophenol in 65 mL of THF, which was added dropwise over a 10-min period. The suspension was stirred for 40 min before a solution of 9.3 g (62.4 mmol) of 3,3-dimethylallyl bromide in 25 mL of THF was added over a 10-min period, while the reaction mixture was maintained at ice-bath temperature. The reaction mixture was stirred for a further 45 min and then allowed to warm to room temperature over a 1.25-h period. The white suspension was poured into 300 mL of water. The organic phase was washed with 150 mL of 1 N NaOH solution and twice with 150 mL of dilute brine and dried (Na_2SO_4, overnight). The colorless solution was concentrated, and the resulting oil was chromatographed on a 5 x 40-cm silica gel column with 2 L of hexane, followed by 1% Et_2O/hexane. The crude allylic sulfide, 3-methyl-2-buten-1-yl phenyl sulfide, was obtained as a colorless oil (10.3 g). This oil was distilled to give 9.76 g (88% yield) of 3-methyl-2-buten-1-yl phenyl sulfide as a colorless, foul-smelling liquid, bp 83-85°C (0.8 mm); IR ($CHCl_3$) 1665, 1580, 1475 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57, 1.70 (2 s, 6, $(CH_3)_2C$), 3.52 (d, J = 8 Hz, 2, CH_2S), 5.30 (t, J = 8 Hz, 1, C=CH), 7.28 (m, 5, ArH); MS calcd for $C_{11}H_{14}S$ 178.081, found 178.080.

6-Acetyl-2,3-dihydro-4,4-dimethyl-1-benzothiopyran. A solution of 1.3 g (16.6 mmol) of acetyl chloride and 2.85 g (16.0 mmol) of 2,3-dihydro-4,4-dimethyl-1-benzothiopyran in 50 mL of CS_2 was added dropwise over a 15-min period to 3.2 g (24.0 mmol) of $AlCl_3$ with stirring and cooling in ice. The additon funnel was rinsed with 10 mL of CS_2. The reaction mixture was stirred at room temperature for 2.25 h, before the resultant orange suspension was treated with 50 mL of ice/brine. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with dilute brine (3 x 50 mL), dried (Na_2SO_4), and concentrated. The pale yellow, viscous oil was chromatographed on a 3 x 30-cm silica gel column with 10% Et_2O/hexane to give 2.92 g (83% yield) of 6-acetyl-2,3-dihydro-4,4-dimethyl-1-benzothiopyran as a pale yellow, viscous liquid; IR ($CHCl_3$) 1670, 1590, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6, $(CH_3)_2C$), 1.93 (m, 2, CCH_2), 2.53 (s, 3, CH_3CO), 3.05 (m, 2, CH_2S), 7.12 (d, J = 8.5 Hz, 1, 8-ArH), 7.57 (dd, J = 8.5, 2 Hz, 1, 7-ArH), 8.00 (d, J = 2 Hz, 1, 5-ArH); UV (MeCN) λ_{max} 237.5 nm (ε 6.3 x 10^3), 242 nm (ε 6.2 x 10^3), 310 nm (ε 1.82 x 10^4); MS calcd for $C_{13}H_{16}OS$ 220.092, found 220.090.

(E)-1-(4-Carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene. To a suspension of NaH, which was obtained from 0.52 g (13 mmol) of 60% NaH/mineral oil dispersion washed three times with 2 mL of hexane, in 20 mL of THF under argon was added at room temperature over a period of 50 min a solution of 2.2 g (10.0 mmol) of 6-acetyl-2,3-dihydro-4,4-dimethyl-1-benzothiopyran, 3.6 g

(12.0 mmol) of diethyl 4-carbethoxybenzyl phosphonate, and 0.45 g (2.0 mmol) of 15-Crown-5 in 30 mL of THF. The orange suspension was stirred at room temperature for 17 h to give a red solution and a red-orange gum. This mixture was treated with 200 g of ice/brine containing 1 mL of HOAc and extracted with Et_2O (2 x 50 mL). The extract was washed with 50 mL of dilute brine, dried (Na_2SO_4), and concentrated. The yellow solid was chromatographed on a 3 x 30-cm silica gel column with 7% Et_2O/hexane to give 3.2 g (87% yield) of the crude product, which was further purified by preparative LC in 7% Et_2O/hexane to give 3.14 g (85% yield) of (E)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene. ^1H NMR and analytical LC (Radialpak B, 5% Et_2O/hexane, 1 mL/min, 280 nm) indicated a single isomer contaminated with an oxidation product. Two crystallizations from 20 to 30 mL of 10% EtOAc/hexane gave 1.70 g (46% yield) of the pure E-ester (E)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene, mp 94-94.5°C. A further 0.56 g (15% yield) was obtained by two more crystallizations of the material recovered from the crystallization mother liquor. The combined yield of white crystals was 2.26 g (62%); LC (Radialpak A, MeCN, 1 mL/min, 280 nm) t_R 7.8 min (100%); LC (Radialpak B, 5% Et_2O/hexane, 1 mL/min, 280 nm) t_R 7.3 min (100%); IR ($CHCl_3$) 1705, 1605, 1475 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6, $(CH_3)_2C$), 1.41 (t, J = 7 Hz, 3, $CH_2\underline{CH_3}$), 1.99 (m, 2, CCH_2), 2.27 (d, J = 1 Hz, $H_3CC{=}C$), 3.05 (m, 2, CH_2S), 4.39 (q, J = 7 Hz, $\underline{CH_2}CH_3$), 6.79 (s, 1, C=CH), 7.09 (d, J = 8 Hz, 1, 8-ArH), 7.21 (dd, J = 8 Hz, J = 2 Hz, 1, 7-ArH), 7.41 (d, J = 8 Hz, 2, ArH m to CO_2Et) 7.51 (d, J = 2 Hz, 1,

5-ArH), 8.04(d, J = 8 Hz, 2, ArH o to CO_2Et); ^{13}C NMR ($CDCl_3$) 14.3, 17.6, 23.1, 30.2, 33.1, 37.7, 60.7, 123.5, 123.8, 125.5, 126.2, 128.0, 128.7, 129.2, 131.2, 139.1, 139.1, 141.5, 142.8, 166.1 ppm; UV (EtOH) λ_{max} 244.5 nm (ε 1.24 x 10^4), 326 nm (ε 2.62 x 10^4); MS calcd for $C_{23}H_{26}O_2S$ 366.165, found 366.163.

(E)-1-(4-Carboxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene. To a degassed (three times, argon) suspension of 1.50 g (4.1 mmol) of the ethyl ester (E)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene in 7.5 mL of EtOH was added a degassed (two times, argon) solution of 0.75 g (11.4 mmol) of 85% KOH in 2.25 mL of water, followed by a 0.5-mL water rinse. The mixture was again degassed (twice) and then heated at reflux in a 100-110°C oil bath for 40 min. The ester dissolved within 15 min to give a pale-yellow solution. The reaction mixture was cooled to room temperature, quenched with a solution of 2 mL of HOAc in 10 mL of water, and then diluted with 10 mL of brine. Because the white, solid carboxylic acid failed to dissolve in Et_2O, it was extracted out with EtOAc (100 mL, then 50 mL). The very pale-yellow extract was washed with dilute brine (2 x 25 mL) and water (25 mL), dried (Na_2SO_4), and concentrated. The almost white powder was recrystallized twice from 60 mL of EtOAc to give 1.05 g (75% yield) of white crystals, mp 217-217.5°C: LC (Radialpak A, 40% H_2O/MeCN, 1 mL/min, 280 nm) t_R 1.6 (0.3%), 2.1 (1.5%), 4.3 min (98.2%); IR (mull) 3200-2200, 1680, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6, $(CH_3)_2C$), 1.99 (m, 2, CCH_2), 2.29 (s, 3, $H_3CC{=}C$), 3.05 (m, 2, CH_2S), 6.80

(s, 1, C=CH), 7.10 (d, J = 8.6 Hz, 1, 8-ArH), 7.22 (dd, J = 8.3, J = 1.7 Hz, 1, 7-ArH), 7.46 (d, J = 8.3 Hz, 2, ArH m to CO_2H), 7.52 (d, J = 1.8 Hz, 1, 5-ArH), 8.11 (d, J = 8.3 Hz, 2, ArH o to CO_2H); ^{13}C NMR ($CDCl_3/Me_2SO-d_6$) 16.5, 21.8, 29.0, 31.9, 36.4, 122.3, 122.7, 124.3, 125.0, 127.4, 127.6, 128.2, 130.0, 137.7, 138.8, 140.4, 141.3, 166.4 ppm; UV (EtOH) λ_{max} 233 nm (ε 1.08 x 10^4), 319 nm (ε 2.53 x 10^4); MS calcd for $C_{21}H_{22}O_2S$ 338.134, found 338.132.

Example 3. Preparation of (E)-1-(4-Carboxyphenyl-2-(4,4 dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene.

2,3-Dihydro-4,4-dimethyl-1-benzopyran was prepared by two routes, both based on reported procedures. Method A as shown on page 16 utilized a Friedel-Crafts alkylation of phenol by diphenyl 3-methyl-3-buten-1-yl phosphate (Butsugan Y., et al, supra). The overall yield from diphenyl chlorophosphate was 39%. Method B as shown on page 17 employed an intramolecular Friedel-Crafts alkylation (Milstien, S., et al, supra) of phenyl 3,3-dimethylacrylate to give the lactone, 2,3-dihydro-4,4-dimethyl-2-oxo-1-benzopyran, which was reduced to the diol (compound 18 on page 17, Borchardt, R.T., et al, supra), and the primary alcohol group of which was selectively esterified as the mesylate. Intramolecular displacement of the mesylate by phenoxide ion gave 2,3-dihydro-4,4-dimethyl-1-benzopyran in 71% overall yield from phenol. Attempted synth sis of 2,3-dihydro-4,4-dimethyl-1-benzopyran by cyclization of 3,3-dimethyl-allyl phenyl ether using a variety of Lewis acids gave littl or none of the desired ether. 2,3-Dihydro-4,4-

(s, 1, C=CH), 7.10 (d, J = 8.6 Hz, 1, 8-ArH), 7.22 (dd, J = 8.3, J = 1.7 Hz, 1, 7-ArH), 7.46 (d, J = 8.3 Hz, 2, ArH m to CO_2H), 7.52 (d, J = 1.8 Hz, 1, 5-ArH), 8.11 (d, J = 8.3 Hz, 2, ArH o to CO_2H); ^{13}C NMR ($CDCl_3/Me_2SO-d_6$) 16.5, 21.8, 29.0, 31.9, 36.4, 122.3, 122.7, 124.3, 125.0, 127.4, 127.6, 128.2, 130.0, 137.7, 138.8, 140.4, 141.3, 166.4 ppm; UV (EtOH) λ_{max} 233 nm (ε 1.08 x 10^4), 319 nm (ε 2.53 x 10^4); MS calcd for $C_{21}H_{22}O_2S$ 338.134, found 338.132.

Example 3. Preparation of (E)-1-(4-Carboxyphenyl-2-(4,4 dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene.

2,3-Dihydro-4,4-dimethyl-1-benzopyran was prepared by two routes, both based on reported procedures. Method A as shown on page 16 utilized a Friedel-Crafts alkylation of phenol by diphenyl 3-methyl-3-buten-1-yl phosphate (Butsugan Y., et al, supra). The overall yield from diphenyl chlorophosphate was 39%. Method B as shown on page 17 employed an intramolecular Friedel-Crafts alkylation (Milstien, S., et al, supra) of phenyl 3,3-dimethylacrylate to give the lactone, 2,3-dihydro-4,4-dimethyl-2-oxo-1-benzopyran, which was reduced to the diol (compound 18 on page 17, Borchardt, R.T., et al, supra), and the primary alcohol group of which was selectively esterified as the mesylate. Intramolecular displacement of the mesylate by phenoxide ion gave 2,3-dihydro-4,4-dimethyl-1-benzopyran in 71% overall yield from phenol. Attempted synthesis of 2,3-dihydro-4,4-dimethyl-1-benzopyran by cyclization of 3,3-dimethyl-allyl phenyl ether using a variety of Lewis acids gave little or none of the desired ether. 2,3-Dihydro-4,4-

dimethyl-1-benzopyran was readily and cleanly acetylated at the 6-position in 81% yield using acetyl chloride and $SnCl_4$. Acylation of chroman at C-6 is well established (Chatelus, G., supra).

The olefin (E)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene was prepared from 6-acetyl-2,3-dihydro-4,4-dimethyl-1-benzopyran by Horner-Emmons reaction using diethyl 4-carbethoxybenzyl phosphonate in the presence of 15-Crown-5 at room temperature. Surprisingly, the reaction was not completely stereoselective.(6) The major, E-isomer was easily isolated in 57% yield by crystallization from hexane. A sample of the minor isomer was obtained by recycle LC (5% Et_2O/hexane) for spectral comparison. The ^1H NMR spectrum of the minor isomer showed significant upfield shifts of the chroman aromatic protons (unresolved multiplets at 60 MHz) and of the gem-dimethyl protons (upfield shift of the minor isomer, 0.26 ppm), due to shielding by the 4-carbethoxyphenyl function. In addition the olefinic proton in this isomer was shifted upfield by 0.33 ppm. A similar shift is observed for cis-stilbene relative to trans-stilbene.(7) The UV absorbtion maxima also support a Z-configuration for the minor isomer; the major isomer had λ_{max} 316 nm (ε 2.42 x 10^4), whereas the minor isomer had λ_{max} 306 nm (ε 1.17 x 10^4).

(6) Baker, R., et al, Angew Chem Int Ed Engl (1981) 20:117.
(7) Katayama, M., t al, J Mol Spectroscopy (1960) 5:85.

2,3-Dihydro-4,4-dimethyl-1-benzopyran.

Method A: To a solution of 8.6 g (0.10 mmol) of 3-methyl-3-buten-1-ol in 100 mL of Et_2O containing 8.3 g (0.105 mol) of pyridine, cooled in ice, was added over a period of 10 min a solution of 26.9 g (0.10 mmol) of diphenyl chlorophosphate in 100 mL of Et_2O. The mixture was stirred at room temperature for 19 h, heated at reflux for 3.25 h, and then cooled. The white suspension was washed with water (2 x 50 mL), dried (Na_2SO_4), and concentrated to give 32.3 g of pale yellow oil. A sample (1.0 g) of the crude product was chromatographed on a 2 x 30-cm silica gel column with 10% EtOAc/hexane to give 0.70 g (71% yield) of diphenyl 3-methyl-3-buten-1-yl phosphate, a colorless oil; IR ($CHCl_3$) 3070, 1650, 1590, 1480, 1280, 1175, 1155, 1020 (1060 sh), 950, 895 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3, $CH_3C=C$), 2.42 (t, J = 7 Hz, 2, $C=CCH_2$), 4.37 (q, J = 7 Hz, 2, CH_2O), 4.78 (m, 2, $H_2C=C$), 7.30 (m, 10, ArH).

To 10.5 g (40 mmol) of $SnCl_4$, cooled in ice, was added 18.8 g (0.20 mol) of phenol with stirring. After 5 min, a yellow liquid was obtained. To this complex was added over a 10-min period, 14.5 g (31.9 mmol) of the crude phosphate followed by a 5-ml CS_2 rinse. The resultant orange syrup was stirred at room temperature for 18 h, poured onto 300 g of ice/brine, and extracted with Et_2O (2 x 300 mL). The extract was washed with 2 N NaOH (2 x 200 mL) and dilute brine (3 x 200 mL), dried ($MgSO_4$), and concentrated to give 8.3 g of cloudy liquid, which was chromatographed on a 4.5 x 40-cm silica g l column with 2% Et_2O/hexan to

give 2.9 g (39% overall yield from diphenyl chlorophosphate) of 2,3-dihydro-4,4-dimethyl-1-benzopyran as a colorless liquid; IR ($CHCl_3$) 1610, 1575, 1480, 1445, 1290, 1245 (1230 sh), 1125, 1065, 945, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 6, $(CH_3)_2C$), 1.80 (t, J = 5.5 Hz, 2, $\underline{CH_2}C(CH_3)_2$), 4.17 (t, J = 5.5 Hz, 2, CH_2O), 7.0 (m, 4, ArH); ^{13}C NMR ($CDCl_3$) 30.5 (C-4), 31.1 ($(\underline{CH_3})_2C$), 37.8 (C-3), 62.9 (C-2), 117.0 (C-8), 120.5 (C-6), 126.9, 127.0 (C-5, C-7), 131.6 (C-4a), 153.7 ppm (C-8a).

Method B: To a degassed (3 times, argon) suspension of NaH, obtained from 2.15 g (54 mmol NaH) of 60% NaH/mineral oil, which had been washed with hexane (3 x 10 mL), in 20 mL of THF was added over a 5-min period with stirring and cooling in ice a solution of 5.0 g (53 mmol) of phenol in 55 mL of THF. The suspension was stirred for a further 10 min, treated with a solution of 7.0 g (59 mmol) of 3,3-dimethylacryloyl chloride in 27 mL of THF over a 5-min period, and then allowed to warm to room temperature over a 3-h period. The suspension was poured into 150 mL of water containing 1 mL of HOAc. The mixture was stirred for 15 min and extracted with 150 mL of Et_2O. The extract was washed with dilute brine (2 x 100 mL) and water (100 mL), dried (Na_2SO_4), and concentrated to give a pale yellow liquid. The ester was chromatographed on a 4 x 45-cm silica gel column with 10% Et_2O/hexane to give 9.2 g (99% yield) of phenyl 3,3-dimethylacrylate as a pale y llow liquid; IR ($CHCl_3$) 1730, 1650, 1495, 1130, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 and 2.22 (2 s, 6, $(CH_3)_2C$), 5.92 (m, 1, C=CH), 7.25 (m, 5, ArH).

This purified ester (9.0 g, 51.1 mmol) in 50 mL of CH_2Cl_2 was added to a stirred, ice-cooled suspension of 12.0 g (90 mmol) of $AlCl_3$ in 200 mL of CH_2Cl_2. This suspension was stirred at room temperature for 63 h to give a dark brown solution, which was poured onto 500 mL of ice/brine and then extracted with 150 mL of CH_2Cl_2. The brown extract, which contained some suspended solid and aqueous emulsion, was filtered to separate out a dark-red organic phase. The organic solution was washed with dilute brine (3 x 250 mL), dried (Na_2SO_4), and concentrated to give a dark-red oil, which was chromatographed on a 4 x 45-cm silica gel column with 10% Et_2O/hexane to give 6.90 g (77% yield) of 2,3-dihydro-4,4-dimethyl-2-oxo-1-benzopyran as a colorless viscous oil; IR ($CHCl_3$) 1765, 1450, 1275, 1180, 1085, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6, $(CH_3)_2C$), 2.60 (s, 3, CH_2CO), 7.20 (m, 4, ArH).

To 5.0 g (132 mmol) of $LiAlH_4$, which was stirred under argon and cooled in an ice bath, was added 75 mL of THF. This suspension was degassed (argon) and then treated with a solution of 6.0 g (34.1 mmol) of 2,3-dihydro-4,4-dimethyl-2-oxo-1-benzopyran in 35 mL of THF. The suspension was refluxed for 2 h and then cooled in ice. The excess $LiAlH_4$ was destroyed by the dropwise addition of 20% EtOAc/THF. The thick suspension was poured into 200 mL of 2 N H_2SO_4/ice. This mixture was saturated with NaCl and extracted with Et_2O (3 x 200 mL). The extract was washed with dilute brine (3 x 100 mL), dried (Na_2SO_4), and concentrated to 6.2 g of white solid, the crude diol (compound 18 on page 17): IR ($CHCl_3$) 3580, 3300, 1440, 1220, cm^{-1}; ^1H NMR ($CDCl_3/Me_2SO$-d_6) δ 1.38 (s, 6, $(CH_3)_2C$), 2.13 (t, J = 7.5 Hz, 2, $CH_2C(CH_3)_2$), 3.35

(t, J = 7.5 Hz, 2, CH_2O), 3.4 (broad s, 1, OH, exchanged D_2O), 6.9 (m, 4, ArH), 8.75 (broad s, 1, ArOH, exchanged D_2O).

A solution of 5.1 g (28.3 mmol) of diol in 60 mL of pyridine was treated with 4.3 g (37.6 mmol) of methanesulfonyl chloride with stirring and cooling in an ice bath and then stirred at ice-bath temperature for 1 h. The mixture was poured into 200 mL of brine and extracted with Et_2O (3 x 100 mL). The extract was washed with dilute brine (100 mL), 1 N HCl solution (2 x 200 mL), and dilute brine (2 x 100 mL), dried ($MgSO_4$, 1 h), and concentrated to give an oil. This crude mesylate ester was dissolved in 60 ML of dioxane and treated with stirring with 75 mL of 1 N NaOH. After being stirred at room temperature for 2.25 h, the two-phase mixture was diluted with brine (100 mL) and extracted with Et_2O (3 x 100 mL). The extract was washed with 75 mL of dilute brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on a 4.5 x 45-cm silica gel column with 3% Et_2O/hexane to give 4.31 g (95% overall yield from 2,3-dihydro-4,4-dimethyl-2-oxo-1-benzopyran) of 2,3-dihydro-4,4-dimethyl-1-benzopyran, which was spectrally identical (IR, ^1H NMR) with the sample prepared by Method A.

6-Acetyl-2,3-dihydro-4,4-dimethyl-1-benzopyran. A solution of 3.6 g (45.9 mmol) of AcCl and 6.5 g (40.1 mmol) of 2,3-dihydro-4,4-dimethyl-1-benzopyran in 80 mL of CS_2 was added dropwise over a period of 25 min to 16 g (61.3 mmol) of $SnCl_4$ with stirring and cooling in an ice bath. The mixture was stirred at room temp rature for 2.25 h to give a blue-purple suspension and then poured into 200 mL of ice/brine.

The resultant purple suspension was shaken with 1 L of saturated $NaHCO_3$ solution and 600 mL of CH_2Cl_2. The aqueous phase was again extracted with CH_2Cl_2 (400 mL), and then combined extracts were washed with $NaHCO_3$ (500 mL), brine (2 x 500 mL), and water (500 mL), and dried (Na_2SO_4). The yellow solution was concentrated to give 8.3 g of an orange-brown, viscous oil, which was chromatographed on a 4.5 x 45-cm silica gel column with 10% EtOAc/hexane to give 6.85 g of a light-green viscous liquid. A 6.0-g sample of this material was purified by bulb-to-bulb distillation at 110-115°C (0.5 mm) to yield 5.82 g (81% yield) of 6-acetyl-2,3-dihydro-4,4-dimethyl-1-benzopyran as a colorless viscous liquid; IR ($CHCl_3$) 1670, 1605, 1495, 1360, 1315, 1245 (1225 sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 6, $(CH_3)_2C$), 1.83 (t, J = 5.5 Hz, 2, $CH_2C(CH_3)_2$), 2.53 (s, 3, CH_3CO), 4.24 (t, J = 5.5 Hz, 2, CH_2O), 6.82 (d, J = 8.5 Hz, 1, H-8), 7.72 (dd, J = 8.5, J = 2 Hz, 1, H-7), 7.98 (d, J = 2 Hz, 1, H-5); UV (MeCN) λ_{max} 222 nm (ε 1.32 x 10^4), 272 nm (ε 1.48 x 10^4); MS calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1146.

(E)-1-(4-Carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene. A degassed (argon), stirred suspension of NaH, obtained from 0.52 g (13 mmol of NaH) of 60% NaH/mineral oil dispersion that was washed with hexane (3 x 3 mL), in 15 mL of THF was treated at room temperature over a 5-min period with a solution of 2.04 g (10 mmol) of 6-acetyl-2,3-dihydro-4,4-dimethyl-1-benzopyran, 3.6 g (12 mmol) of diethyl 4-carboxybenzyl phosphonate, and 0.45 g (2.0 mmol) of 15-Crown-5 in 35 mL of THF. The suspension was stirred at room temperature for 16 h to give a red gum and a red solution. The reaction

mixture was treated with 200 mL of brine containing 1 mL of HOAc and extracted with Et_2O (2 x 150 mL). The extract was washed with water (150 mL), dried (Na_2SO_4), and concentrated. The yellow oil was eluted through a 4.5 x 35-cm silica gel column with 7% Et_2O/hexane to give 3.0 g of an almost colorless gum; LC (Radialpak B, 5% Et_2O/hexane, 1 mL/min, 280 nm) t_R 7.3 (84.5%), 8.6 min (15.5%). Two crystallizations of this product from hexane (4 mL, then 3 mL) gave 1.98 g (57% yield) of (E)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene as white needles, mp 70-71.5°C; LC (Radialpak A, MeCN, 1 mL/min, 280 nm) t_R 6.2 (98.3%), 7.0 min (1.7%); LC (Radialpak B, 5% Et_2O/hexane, 1 mL/min, 280 nm) t_R 7.4 (99.7%), 8.6 min (0.3%); IR ($CHCl_3$) 1700, 1605, 1490, 1280, 1230, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6, $(CH_3)_2C$), 1.40 (t, J = 7.5 Hz, 3, $CH_2\underline{CH_3}$), 1.85 (t, J = 5.5 Hz, 2, $\underline{CH_2}C(CH_3)_2$), 2.28 (s, 3, $\underline{CH_3}C{=}CH$), 4.23 (t, J = 5.5 Hz, 2, CH_2O), 4.40 (q, J = 7.5 Hz, 2, $\underline{CH_2}CH_3$), 6.78 (s, 1, C=CH), 6.82 (d, J = 8.5 Hz, 1, 8-Ar), 7.2-7.5 (m, 2, 5,7-Ar), 7.45 (d, J = 8.5 Hz, 2, ArH m to $CO_2CH_2CH_3$), 8.08 (d, J = 8.5 Hz, 2, ArH o to $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) 14.7, 18.0, 31.0, 31.3, 37.9, 61.1, 63.3, 117.1, 124.7, 125.1, 125.4, 128.3, 129.2, 129.7, 131.6, 136.0, 139.7, 143.6, 153.7, 166.8 ppm (C=O); UV (EtOH) λ_{max} 236 nm (ε 1.41 x 10^4), 316 nm (ε 2.42 x 10^4); MS calcd for $C_{23}H_{26}O_3$ 350.1882, found 350.1893.

A sample of the gum obtained by concentration of the crystallization mother liquors was purified using the LC recycle technique (Et_2O/hexane) to give an impure sample of (Z)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene as a very pale-yellow gum; LC (Radialpak B, 5%

EtO/hexane, 1 mL/min, 280 nm) t_R 7.2 (7.4%), 8.4 min (92.6%); IR ($CHCl_3$) 1705, 1605, 1495, 1370, 1280, (1230 sh), 1110, 910, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 6, $(CH_3)_2C$), 1.31 (t, J = 7.5 Hz, 3, $CH_2\underline{CH_3}$), 1.77 (t, J = 5.5 Hz, 2, $\underline{CH_2}C(CH_3)_2$), 2.20 (d, J = 1.5 Hz, 3, $\underline{CH_3}C{=}CH$), 4.15 (t, J = 5.5 Hz, 2, CH_2O), 4.32 (q, J = 7.5 Hz, 2, $\underline{CH_2}CH_3$), 6.45 (s, 1, C=CH), 6.65-7.2 (m, 5, 5,7,8-ArH, ArH m to $CO_2CH_2CH_3$), 7.85 (d, J = 8.5 Hz, 2, ArH o to $CO_2CH_2CH_3$); UV (EtOH) λ_{max} 244 nm (ε 1.69 x 10^4), 306 nm (ε 1.17 x 10^4); MS calcd for $C_{23}H_{26}O_3$ 350.1882, found 350.1887.

(E)-1-(4-Carboxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene. A degassed (argon) solution of 0.6 g (9.1 mmol) of 85% KOH in 5 mL of EtOH and 1 mL of H_2O was added to 1.15 g (3.19 mmol) of (E)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene. The mixture was degassed (argon) and heated in a 110°C oil bath for 65 min to give a clear solution. The cold white suspension was diluted with 5 mL of 50% HOAc and 50 mL of brine. The product was extracted into 500 mL of 50% Et_2O/THF. The extract was washed with dilute brine (2 x 100 mL), dried ($MgSO_4$), and concentrated. The white solid was dissolved in 250 mL of 50% EtOAc/C_6H_6 at reflux. The hot solution was filtered through a glass wool plug, concentrated to 100 mL, and cooled to -5°C to give 0.976 g (92% yield) of product as white crystals, mp 285-286°C; LC (Radialpak A, MeOH, 1 mL/min, 260 nm) t_R 3.3 min (100%); IR (mull) 3500, 2300, 1675, 1625, 1470, 1375, 1300, 1280, 1230, 820 cm^{-1}; 300 MHz ^1H NMR (M$_2$SO) δ 1.40 (s, 6, $(CH_3)_2C$), 1.84 (m, 2, CH_2C), 4.20 (m, 2, CH_2O), 6.88 (d, J = 8.4 Hz, 1, H-8), 7.55 (dd, J = 8.5 Hz, J = 2.1 Hz, 1, H-7), 7.80

(d, J = 2.1 Hz, 1, H-5), 7.91 (dd, J = 8 Hz, J=1.4 Hz, 1, napH-7), 7.99 (dd, J = 8 Hz, J = 0.8 Hz, 1, napH-4 or napH-8), 8.07 (d, J = 8.7 Hz, 1, napH-4 or napH-8), 8.16 (d, J = 8.6 Hz, 1, napH-3), 8.24 (s, 1, napH-5), 8.61 (s, 1, napH-1); ^{13}C NMR (Me_2SO-d_6/$CDCl_3$) 28.5, 28.8, 35.2, 60.7, 115.4, 122.1, 123.6, 123.9, 125.8, 126.2, 127.8, 128.4, 129.0, 129.8, 130.1, 133.6, 138.1, 151.6, 165.6 ppm; UV (95% EtOH) λ_{max} 232 nm (ε 4.96×10^4), 268 nm (ε 3.31×10^4), 314 nm (ε 2.11×10^4); MS calcd for $C_{22}H_{20}O_3$ 332.1412, found 332.1410; Anal. calcd for $C_{22}H_{20}O_3$: C 79.49, H 6.06; found: C 79.84, H 6.34.

Example 4. (E)-1-(4-Carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene and (E)-1-(4-Carboxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene

1,2,3,4-Tetrahydro-1,4-methano-6-naphthoic Acid. To a solution of 60 g (1.5 mol) of NaOH in 300 mL of H_2O cooled to -5°C was added 25.6 mL (0.5 mol) of Br_2 over a period of 5 min. The resulting solution of NaOBr was kept below 0°C, while a solution of 18.6 g (0.1 mol) of 1,2,3,4-tetrahydro-6-acetyl-1,4-methano-naphthalene in 10 mL of dioxane was added. The temperature of the reaction mixture was gradually raised to 60-65°C with a hot-water bath and was maintained there for 0.5 h. The reaction mixture was then cooled to room temperature, before a solution of 50 g (0.48 mol) of $NaHSO_3$ in 200 mL of H_2O was added. The yellow reaction mixture turned colorless. The mixture was acidified with about 120 mL of concentrated HCl; and the white, precipitated acid was extracted into 800 mL of Et_2O. The ethereal solution

was dried (Na_2SO_4) and concentrated. The crude product was recrystallized (three crops) from EtOAc to give a total of 17.67 g (94% yield) of the acid as white needles, mp 153-154°C; IR (mull) 2900-3200 (CO_2H), 1680, 1280, 1110, 950, 860, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1-2.2 (m, 6, $(CH_2)_2$, CH_2), 3.45 (s, 2, 2 CH), 7.2-7.4 and 7.9-8.15 (2 m, 3, ArH), 11.65 (broad s, 1, CO_2H); MS calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0818.

1,2,3,4-Tetrahydro-6-formyl-1,4-methanonaphthalene. The naphthoic acid prepared as described above (9.4 g, 0.05 mol) was added slowly to a stirred suspension of 1.0 g (26.4 mmol) of $LiAlH_4$ in 100 mL of THF. Another 0.6-g (15.8 mmol) portion of $LiAlH_4$ was then added. This mixture was stirred at room temperature for 2 h, when TLC (25% EtOAc/hexane) indicated that no starting material remained. To the reaction mixture was slowly added 1.6 mL of H_2O, 4.8 mL of 15% aqueous NaOH, and 1.6 mL of H_2O. The mixture was filtered through Celite (100-mL Et_2O wash). The filtrate was concentrated, and the resulting colorless oil was purified by chromatography on 150 g of silica gel (30% Et_2O/hexane) to give 8.8 g (100% yield) of 1,2,3,4-tetrahydro-6-hydroxymethyl-1,4-methanonaphthalene as a colorless oil: IR (film) 3200-3600 (OH), 3000, 2900, 1500, 1460, 1440, 1300, 1270, 1240, 1200, 1140, 1090, 1020, 960, 900, 880, 830, 770, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95-2.0 (m, 6, $(CH_2)_2$, CH_2), 2.93 (s, 1, OH), 3.15-3.40 (m, 2, 2 CH), 4.48 (s, 2, CH_2OH), 6.9-7.25 (m, 3, ArH); MS calcd for $C_{12}H_{14}O$ 174.1045, found 174.1058.

A solution of 50 mL (0.62 mol) of pyridine in 250 mL of CH_2Cl_2 was cooled in an ice-bath while

31 g (0.31 mol) of CrO_3 was added in several portions over a period of 30 min. The mixture was stirred for another 15 min. Then 8.6 g (0.15 mol) of 1,2,3,4-tetrahydro-6-hydroxymethyl-1,4-methanonaphthalene in 5 mL of CH_2Cl_2 was added. This mixture was stirred at 0°C for 20 min when TLC (25% Et_2O/hexane) indicated that reaction was complete. The reaction mixture was filtered through Florisil (500 mL of CH_2Cl_2 wash). The filtrate was concentrated and passed over 200 g of silica gel (25% Et_2O/hexane) to give 6.8 g (80% yield of 1,2,3,4-tetrahydro-6-formyl-1,4-methanonaphthalene as a pale yellow oil: IR (film) 3000, 2900, 2800, 2750, 1700, 1620, 1590, 1460, 1440, 1360, 1310, 1230, 1190, 1140, 1080, 1030, 960, 840, 810, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1-2.1 (m, 6, $(CH_2)_2$, CH_2), 3.45 (broad s, 2, 2 CH), 7.3-7.8 (m, 3, ArH), 10.0 (s, 1, CHO); MS calcd for $C_{12}H_{12}O$ 172.0888, found 172.0898.

(E)-1-(4-Carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydronaphth-6-yl)ethene. A 1.06-g (27.4 mmol) portion of NaH-mineral oil dispersion (59.3%) was washed with three 10-mL portions of pentane, and the resulting powder was suspended in 100 mL of THF. A mixture of 4.7 g (27.3 mmol) of 1,2,3,4-tetrahydro-6-formyl-1,4-methanonaphthalene, 8.19 g (27.3 mmol) of diethyl 4-carbethoxybenzyl phosphonate, and 100 mg of 15-crown-5 in 25 mL of THF was added. Hydrogen gas slowly evolved. The reaction mixture was stirred at room temperature for 2 h, and then diluted with 300 mL of H_2O and extracted with Et_2O (3 x 100 mL). The ethereal extracts wer washed with brine (2 x 200 mL), dried (Na_2SO_4), and concentrated at reduced pressure to give a white solid, which was recrystallized from

EtOAc to give 7.7 g (88% yield) of white crystals, mp 113-114°C; LC (Radialpak B, 2% Et_2O/hexane, 2 mL/min, 260 nm) t_R 12.8 min (100%); LC (Radialpak A, 10% H_2O/MeCN, 2 mL/min, 260 nm), t_R 7.55 min (100%); IR (mull) 1710, 1610, 1420, 1290, 1190, 1120, 1030, 970, 860, 780 cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 8 Hz, 2, endo-2,3-H), 1.40 (t, J = 7 Hz, 3, $CO_2CH_2\underline{CH_3}$), 1.55 (d, J = 8 Hz, 1, anti-9-H), 1.77 (d, J = 1, syn-9-H), 1.94 (d, J = 8 Hz, 2, exo-2,3-H), 3.38 (broad s, 2, 1,4-H), 4.38 (q, J = 7 Hz, 2, $CO_2\underline{CH_2}CH_3$), 7.07 (d, J = 16 Hz, 1, C-2 HC=CH, 7.16 and 7.22 (2 d, J = 9 Hz, 2, 7,8-H), 7.20 (d, J = 16 Hz, 1, C-1 HC=CH, 7.40 (s, 1, 5-H), 7.54 (d, J = 8 Hz, 2, 2', 6'-H), 8.01 (d, J = 8 Hz, 2, 3', 5'-H); 100 MHz ^{13}C NMR ($CDCl_3$) 14.3 (CH_3), 27.0 and 27.1 (2, 3), 43.5 and 43.6 (1, 4), 49.0 (9), 60.8 ($\underline{CH_2}CH_3$), 118.2, 120.7 125.1, 126.0 (2', 6'), 128.8, 129.9 (3', 5'), 131.9, 134.2, 142.1, 148.8, 148.9, 166.4 ppm (CO_2); UV (EtOH) λ_{max} 208 nm (ε 2.29 x 10^4), 238 nm (ε 1.27 x 10^4), 332 nm (ε 4.04 x 10^4); MS calcd for $C_{22}H_{22}O_2$ 318.1620, found 318.1607.

(E)-1-(4'-Carboxyphenyl)-2-(1,2,3,4-tetrahydro-1,4-methanonaphth-6-yl)ethene. To a suspension of 1.5 g (4.7 mmole) of ester prepared as described above in 10 mL of EtOH was added a solution of 1.2 g (21.4 mmole) of KOH in 5 mL of H_2O and 3 mL of EtOH. The mixture was degassed three times and stirred at 80°C for 40 min under an argon atmosphere. Th cooled reaction mixture was acidified with 18 mL of a 1:1 mixture of HOAc and H_2O. The precipitated acid was collected by filtration and was recrystallized from EtOH to give 1.05 g (77% yield) of the acid as

white plates, mp 275°C; LC (Radialpak A, 0.1% TFA in 25% H_2O/MeCN, 2 mL/min, 280 nm) t_R 5.38 min (0.1%), 5.83 min (99.9%); IR (mull) 2900-3200, 1690, 1620, 1440, 1340, 1300, 1190, 1120, 960, 890, 860, 830, 800, 780 cm^{-1}; 300 MHz ^1H NMR (Me_2SO-d_6) δ 1.10 (d, J = 8 Hz, 2, endo-2,3-H), 1.54 (d, J = 8 Hz, 1, anti-9-H), 1.67 (d, J = 1, syn-9-H), 1.91 (d, J = 8 Hz, 2, exo-2,3-H), 3.32 (s, 2, 1, 4-H), 7.18 and 7.27 (2 d, J = 8 Hz, 2, 7,8-H), 7.22 and 7.35 (2 d, J = 16 Hz, 2, HC=CH), 7.50 (s, 1, 5-H), 7.67 (d, J = 8 Hz, 2, 2',6'-H), 7.92 (d, J = 8 Hz, 2, 3',5'-H), 12.84 (broad s, 1, COOH); 100 MHz ^{13}C NMR (Me_2SO-d_6) 26.7 (2, 3), 42.9 and 43.0 (1, 4), 48.5 (9), 118.2, 120.6, 125.2, 125.7, 126.2 (2', 6'), 129.1, 129.7 (3', 5'), 131.7, 134.1, 141.7, 148.3, 148.4, 167.1 ppm (CO_2); UV (EtOH) λ_{max} 209 nm (ε 2.31 x 10^4), 236 nm (ε 1.29 x 10^4), 326 nm (ε 3.90 x 10^4;; MS calcd for $C_{20}H_{18}O_2$ 290.1307, found 290.1312.

The retinoids of formula (1) may be used topically or systemically as chemopreventive agents and in the treatment, amelioration, or prevention of the skin, rheumatic and other disorders for which retinoic acid and other retinoids are useful. In this regard, they may be used for therapy in animals, including humans, of premalignant epithelial cell lesions, as a prophylaxis against tumor promotion in epithelial cells and treatment for dermatoses such as icthyoses, follicular disorders, benign epithelial disorders, and other proliferative skin diseases (non-malignant conditions of the skin that are character-ized by epidermal cell proliferation or incomplete cell differentiation) such as acne, psoriasis, eczema, atopic dermatitis, nonspecific dermatitis and the

like. When used for such treatments they will usually be formulated with a pharmaceutical liquid, semi-solid, or solid carrier. A pharmaceutically acceptable carrier is a material that is nontoxic and generally inert and does not affect the functionality of the active ingredients adversely. Such materials are well known and include those materials sometimes referred to as diluents or vehicles in the pharmaceutical formulation art. The carrier may be organic or inorganic in nature. Examples of pharmaceutically acceptable carriers that may be used to formulate the retinoids are water, gelatin, lactose, starch, mineral oil, cocoa butter, dextrose, sucrose, sorbitol, mannitol, gum acacia, alginates, cellulose, talc, magnesium stearate, polyoxyethylene sorbitan monolaurate, and other commonly used pharmaceutical carriers. In addition to the retinoid and carrier the formulation may contain minor amounts of additives such as flavoring agents, coloring agents, thickening or gelling agents, emulsifiers, wetting agents, buffers, stabilizers, and preservatives such as antioxidants.

For topical administration the retinoids are conveniently provided in the form of ointments, tinctures, creams, solutions, lotions, sprays, suspensions, and the like. The amount of retinoid in such topical formulations will normally be in the range of about 0.01 to about 1% by weight. For enteral (oral or rectal) administration the retinoids will typically be formulated as tablets, capsules, dragees, syrups, solutions, or suppositories. For parenteral administration the retinoids will be formulated as injectable solutions or suspensions.

The dosages and dosage regimen in which the retinoids are administered will vary according to the

dosage form, mode of administration, the condition being treated and particulars of the patient being treated. They will, of course, be administered in chemopreventive (tumor promotion inhibiting) amounts or therapeutically effective amounts. For adult humans such chemopreventive amounts will usually be about 0.01 mg to 10.0 mg daily given in one or more doses. Oral doses will generally be more than topical doses and doses for treating skin disorders will typically be less than doses administered for cancer chemoprevention. The dose for treating skin disorders will be on the order of, but normally less than, the dose of retinoic acid prescribed for the disorder.

The usefulness of the invention compounds was demonstrated by testing the compounds of the Examples in the ornithine decarboxylase (ODC) assay, Verma, A.K. and Boutwell, R.K., Cancer Res (1977) 37:2196-2201, and the tracheal organ culture assay, Newton, D.L.; Henderson, W.R.; and Sporn, M.B., Cancer Res (1980) 40:3413-3425. The ODC assay measures a compound's ability to prevent the induction of ODC. The tracheal organ culture assay measures a compound's ability to reverse keratinization.

The ODC assay is carried out as follows. Female Charles River CD-1 mice from Charles River Breeding Laboratories, Wilmington, Massachusetts, are used (age 7 to 9 weeks). The dorsal hair of the mice is shaved 1 to 2 days before testing, and only mice showing no hair regrowth are used. A single dose of 12-O-tetradecanoylphorbol-13-acetate (TPA) (10.5 µg, 17 nmol) in 0.2 mL of acetone is applied topically to the back of each mouse. The test compound, at one of three dose levels (1.7, 17 and 170 nmol), dissolved in 0.2 mL of acetone is applied 1 hour before the TPA

treatment to the test groups; the control group is treated with acetone alone. The mice are killed by cervical dislocation five hours after TPA treatment. Determinations are done in triplicate.

The epidermis is obtained from the sacrificed animals. To obtain sufficient material, the dorsal skins from 2 to 3 mice in each treatment group are pooled. The depilatory agent Nudit® (Helena Rubinstein, New York) is applied to the shaved area of the skin; after 5 minutes, it is washed off thoroughly with cold tap water. Then the skin is excised and plunged immediately into ice-cold water; it is then placed in a 55°C water bath for 30 seconds and reimmersed in ice-cold water for at least another 30 seconds. The skin is placed epidermis side up on a cold plate, and the epidermis is scraped off with a razor blade. The pooled epidermal sheets are homogenized (Polytron PT-10 homogenizer) at 0° to 4°C for 15-20 seconds in 50 mM sodium phosphate and 0.1 mM ethylenediaminetetraacetic acid (EDTA), at a volume of 1 mL/skin.

The supernatant fraction remaining after centrifugation of the homogenate at 10,000 x g for 30 seconds at 0°C is used for the enzyme assay. Enzyme activity is determined using the microassay for ODC as described by Verma and Boutwell to measure the release of $^{14}CO_2$ from DL-[1-^{14}C]-ornithine (58 mCi/mmol) after incubation with the 10,000 x g supernatant. The incubations are carried out by decanting, with a Pasteur pipette, 100 µL of the supernatant containing 100 to 120 µg of prot in into two or three 15-mL Corex tubes in a shaking water bath at 37°C. The assay mixture in the tubes consists of 50 µL of 100 mM sodium phosphate buffer (pH 7.2), 10 µL of 4 mM pyridoxal phosphate,

40 μL of 25 mM dithiothreitol, and 1 μL of 0.1 M EDTA. The center wells in the tubes are filled with 200 μL of a 2:1 solution (v/v) of ethanolamine:2-methoxyethanol. The reaction is started by adding 50 μL of substrate (0.5 μCi of DL-[1-^{14}C]-ornithine in 2 mM cold ornithine) at 1-minute intervals by injection to each of the stoppered tubes. Incubations are routinely carried out at 37°C for 30 to 60 minutes. The reaction is stopped by addition of 0.5 ml of 2 M citric acid, and incubation is continued for an additional hour without heating to ensure complete absorption of $^{14}CO_2$.

Radioactivity is measured using a toluene-based scintillant (4 g of PPO and 50 mg of POPOP/L of toluene) in a Beckman LS-250 liquid scintillation counter. Enzyme activity is determined in triplicate and expressed as nanomoles of CO_2 released in 30 minutes per milligram of protein. Enzyme activity is linear for the protein concentration used. The protein concentrations of the epidermal extracts are determined by the Lowry procedure, using bovine serum albumin as the standard.

The tracheal organ culture assay is carried out as follows. Tracheas are taken from hamsters that are in very early stages of vitamin A deficiency and placed in organ culture. At the time of culture, the animals are still gaining weight; the tracheal epithelium is generally low columnar or cuboidal, with only occasional patches of squamous metaplasia. Each trachea is opened from th larynx to the carina along th membranous dorsal wall and cultured in a serum-free medium (CMRL-1066; with crystalline bovine insulin, 0.1 μg/ml; hydrocortisone hemisuccinate, 0.1 μg/ml; glutamin , 2 mM; penicillin, 100 units/ml;

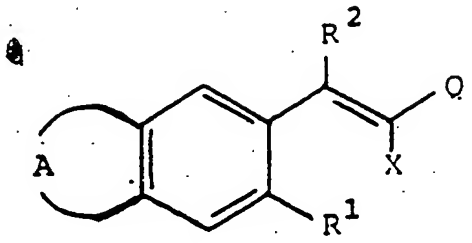
and streptomycin, 100 µg/ml, added). Cultures are gassed with 50% oxygen, 45% nitrogen, and 5% CO_2. The culture dishes are rocked at 35.5-36.0 degrees to allow the tracheas contact with both gas and medium. All tracheas are grown in medium containing no retinoid for the first 3 days. At the end of 3 days, some tracheas are harvested; almost all of these tracheas have significant squamous metaplasia, and approximately 60% have keratinized lesions. The remaining tracheas are then divided into different groups which are treated with either: 1) retinoid dissolved in dimethylsulfoxide (final concentration of DMSO in culture medium is never greater than 0.1%) or 2) an equivalent amount of DMSO alone. Culture medium is changed three times a week, and all of the remaining tracheas are harvested at the end of 10 days in culture. Tracheas are fixed in 10% buffered formalin and embedded in paraffin. Cross sections of five micrometers are made through the mid-portion, stained with hematoxylin and eosin, and then scored with a microscope for the presence of keratin and keratohyaline granules, both of which are found in approximately 90% of control cultures that received no retinoid for the entire 10 day culture period. Retinoids are scored as "inactive" if both keratin and keratohyaline granules are seen; they are scored as "active" if neither keratin nor keratohyaline granules are seen, or if keratohyaline granules alone are absent.

The table below gives the results of these tests.

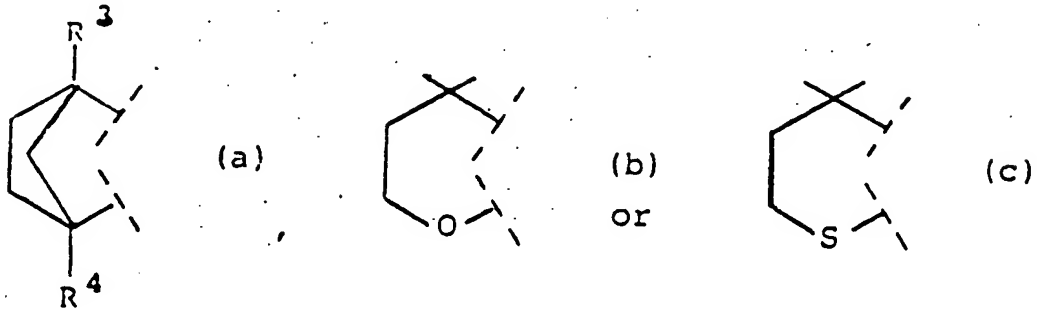
Test Compounds	Reversal of Keratinization in Hamster Tracheal Organ Culture		Inhibition of Induction of Ornithine Decarboxylase by 12-O-Tetradecanoylphorbol-13-acetate in Mouse Skin	
	Conc (M)	Active/Total Cultures (%)	Dose (nmol)	% Inhibition of control
(E)-1-(4-carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene	10^{-8}	7/7 (100)	17	71
	10^{-9}	10/14 (71)	1.7	60
	10^{-10}	4/12 (33)		
	10^{-11}	2/7 (29)		
(E)-1-(4-carboxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-1-propene	10^{-8}	8/8 (100)	17	70
	10^{-9}	8/14 (57)	1.7	34
	10^{-10}	3/14 (21)		
(E)-1-(4-carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)ethene	10^{-8}	4/7 (57)	17	39
	10^{-9}	3/7 (43)	1.7	15
	10^{-10}	1/6 (17)		
(E)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene	10^{-8}	7/7 (100)	17	73
	10^{-9}	6/7 (86)	1.7	46
	10^{-10}	4/7 (56)		
(E)-1-(4-carboxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzothiopyran-6-yl)-1-propene	10^{-8}	7/7 (100)	17	85
	10^{-9}	7/7 (100)	1.7	68
	10^{-10}	6/6 (100)		
(E)-1-(4-carbethoxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene	10^{-8}	7/7 (100)	17	81
	10^{-9}	7/7 (100)	1.7	44
	10^{-10}	2/6 (33)		
(E)-1-(4-carboxyphenyl)-2-(4,4-dimethyl-2,3-dihydro-1-benzopyran-6-yl)-1-propene			17	80
			1.7	37

Claims

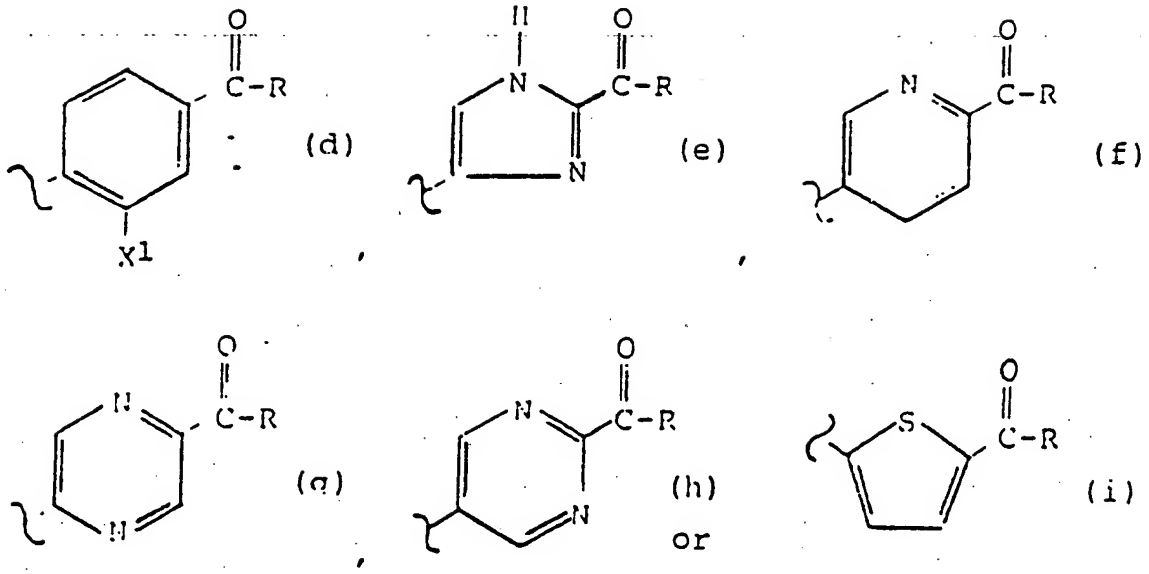
1. A compound of the formula:



where A is the substituent system of a fused ring selected from:



and R^1, R^2, R^3 and R^4 are hydrogen or methyl, X is hydrogen or fluorine and Q is:



where X^1 is hydrogen, hydroxy, methoxy or fluorine, R is hydroxy, alkoxy with 0 or 1 hydroxy substituent, aroxy or NR^5R^6, where R^5 is hydrogen, alkyl with 0 or 1 hydroxy substituent or aryl, and R^6 is alkyl with 0 or 1 hydroxy substituent or aryl, with the provisos that X is fluorine only when R^2 is methyl, when R^3 or R^4 is methyl the other R^3 or R^4 is also methyl, and when Q is (i) Q may be in either the cis or trans position.

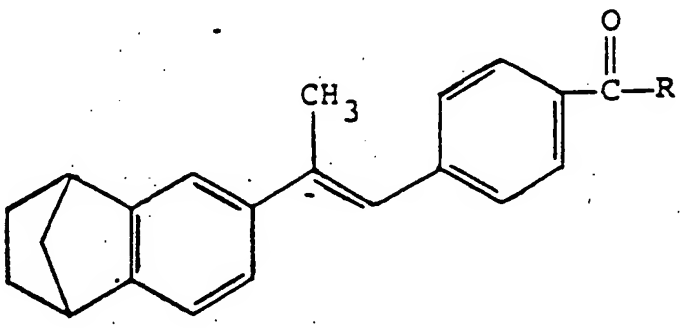
2. The compound of claim 1 wherein the alkoxy group represented by R contains 1 to about 10 carbon atoms with 0 or 1 hydroxy substituent, the aroxy group represented by R contains 6 to about 15 carbon atoms, the alkyl groups represented by R^5 and R^6 each contain 1 to about 8 carbon atoms with 0 or 1 hydroxy substituent and the aryl groups represented by R^5 and R^6 each contain 6 to about 15 carbon atoms with 0 or 1 hydroxy substitu nts.

3. The compound of claim 1 wherein the alkoxy group represented by R contains 1 to 4 carbon atoms with 0 or 1 hydroxy substituent, the aroxy group

represented by R is phenoxy, monohydroxyphenoxy, or monoalkoxyphenoxy, where the alkoxy group contains 1 to 4 carbon atoms, the alkyl groups represented by R^5 and R^6 each contain 1 to 4 carbon atoms and have 0 or 1 hydroxy substituent and the aryl groups represented by R^5 and R^6 are phenyl, 4-hydroxyphenyl, or 4-methoxyphenyl.

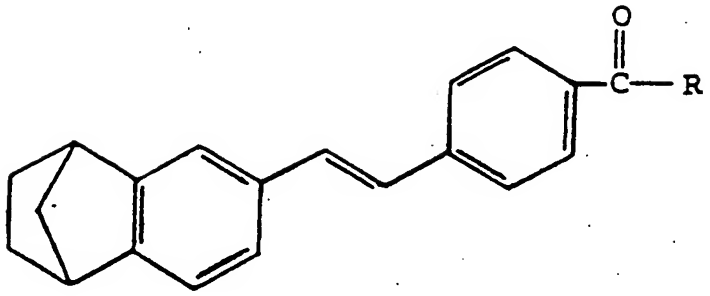
4. The compound of claim 1 where R is ethoxy or hydroxy.

5. A compound of the formula:



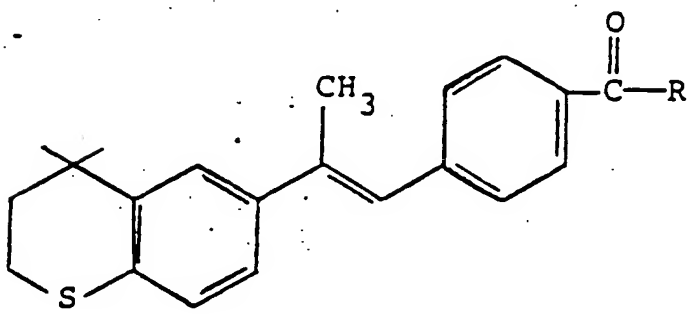
where R is ethoxy or hydroxy.

6. A compound of the formula:



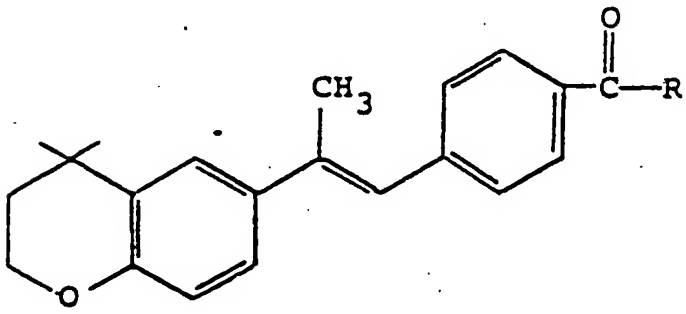
where R is ethoxy or hydroxy.

7. A compound of the formula:



where R is ethoxy or hydroxy.

8. A compound of the formula:



where R is ethoxy or hydroxy.

9. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound of

claim 1 combined with a pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound of claim 2 combined with a pharmaceutically acceptable carrier.

11. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound of claim 3 combined with a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound of claim 4 combined with a pharmaceutically acceptable carrier.

13. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound of claim 5 combined with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound of claim 6 combined with a pharmaceutically acceptable carrier.

15. A pharmac utical composition comprising a pharmaceutically ffective amount of the compound of claim 7 combined with a pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound of claim 8 combined with a pharmaceutically acceptable carrier.

17. A chemopreventive composition for inhibiting tumor promotion in epithelial cells in a living animal comprising a tumor promotion inhibiting amount of the compound of claim 1 combined with a pharmaceutically acceptable carrier.

18. A chemopreventive composition for inhibiting tumor promotion in epithelial cells in a living animal comprising a tumor promotion inhibiting amount of the compound of claim 2 combined with a pharmaceutically acceptable carrier.

19. A chemopreventive composition for inhibiting tumor promotion in epithelial cells in a living animal comprising a tumor promotion inhibiting amount of the compound of claim 3 combined with a pharmaceutically acceptable carrier.

20. A chemopreventive composition for inhibiting tumor promotion in epithelial cells in a living animal comprising a tumor promotion inhibiting amount of the compound of claim 4 combined with a pharmac utically acceptable carrier.

21. A chemopreventive composition for inhibiting tumor promotion in pithelial cells in a living animal comprising a tumor promotion inhibiting amount of the compound of claim 5 combined with a pharmaceutically acceptable carrier.

22. A chemopreventive composition for inhibiting tumor promotion in epithelial cells in a living animal comprising a tumor promotion inhibiting amount of the compound of claim 6 combined with a pharmaceutically acceptable carrier.

23. A chemopreventive composition for inhibiting tumor promotion in epithelial cells in a living animal comprising a tumor promotion inhibiting amount of the compound of claim 7 combined with a pharmaceutically acceptable carrier.

24. A chemopreventive composition for inhibiting tumor promotion in epithelial cells in a living animal comprising a tumor promotion inhibiting amount of the compound of claim 8 combined with a pharmaceutically acceptable carrier.

25. A therapeutic composition for treating a nonmalignant skin disorder comprising a therapeutically effective amount of the compound of claim 1 combined with a pharmaceutically acceptable carrier.

26. A therapeutic composition for treating a nonmalignant skin disorder comprising a therapeutically effective amount of the compound of claim 2 combined with a pharmaceutically acceptable carrier.

27. A therap utic composition for treating a nonmalignant skin disorder comprising a therapeutically effective amount of the compound of claim 3 combined with a pharmaceutically acceptable carrier.

28. A therapeutic composition for treating a nonmalignant skin disorder comprising a therapeutically effective amount of the compound of claim 4 combined with a pharmaceutically acceptable carrier.

29. A therapeutic composition for treating a nonmalignant skin disorder comprising a therapeutically effective amount of the compound of claim 5 combined with a pharmaceutically acceptable carrier.

30. A therapeutic composition for treating a nonmalignant skin disorder comprising a therapeutically effective amount of the compound of claim 6 combined with a pharmarceutically acceptable carrier.

31. A therapeutic composition for treating a nonmalignant skin disorder comprising a therapeutically effective amount of the compound of claim 7 combined with a pharmaceutically acceptable carrier.

32. A therapeutic composition for treating a nonmalignant skin disorder comprising a therapeutically effective amount of the compound of claim 8 combined with a pharmaceutically acceptable carrier.

33. A method of inhibiting tumor promotion in epithelial cells of a human or other living animal comprising administering a tumor promotion inhibiting amount of the compound of claim 1 to the animal.

34. A method of inhibiting tumor promotion in epithelial cells of a human or other living animal comprising administering a tumor promotion inhibiting amount of th compound of claim 2 to the animal.

35. A method of inhibiting tumor promotion in epithelial cells of a human or other living animal comprising administering a tumor promotion inhibiting amount of the compound of claim 3 to the animal.

36. A method of inhibiting tumor promotion in epithelial cells of a human or other living animal comprising administering a tumor promotion inhibiting amount of the compound of claim 4 to the animal.

37. A method of inhibiting tumor promotion in epithelial cells of a human or other living animal comprising administering a tumor promotion inhibiting amount of the compound of claim 5 to the animal.

38. A method of inhibiting tumor promotion in epithelial cells of a human or other living animal comprising administering a tumor promotion inhibiting amount of the compound of claim 6 to the animal.

39. A method of inhibiting tumor promotion in epithelial cells of a human or other living animal comprising administering a tumor promotion inhibiting amount of the compound of claim 7 to the animal.

40. A method of inhibiting tumor promotion in epithelial cells of a human or other living animal comprising administering a tumor promotion inhibiting amount of th compound of claim 8 to the animal.

41. A method of treating a human or other living animal for a nonmalignant skin disorder comprising administering a therapeutically effective amount of the compound of claim 1 to the animal.

42. A method for treating a human or other living animal for a nonmalignant skin disorder comprising administering a therapeutically effective amount of the compound of claim 2 to the animal.

43. A method for treating a human or other living animal for a nonmalignant skin disorder comprising administering a therapeutically effective amount of the compound of claim 3 to the animal.

44. A method for treating a human or other living animal for a nonmalignant skin disorder comprising administering a therapeutically effective amount of the compound of claim 4 to the animal.

45. A method for treating a human or other living animal for a nonmalignant skin disorder comprising administering a therapeutically effective amount of the compound of claim 5 to the animal.

46. A method for treating a human or other living animal for a nonmalignant skin disorder comprising administering a therapeutically effective amount of the compound of claim 6 to the animal.

47. A method for treating a human or other living animal for a nonmalignant skin disorder comprising administering a therapeutically effective amount of the compound of claim 7 to the animal.

48. A method for treating a human or other living animal for a nonmalignant skin disorder comprising administering a thrapeutically effective amount of the compound of claim 8 to the animal.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 84/00280 (SA 6784)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/07/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0084667	03/08/83	AU-A-	1069583	28/07/83
		DE-A-	3202100	04/08/83
		JP-A-	58128340	30/07/83
		DE-A-	3202065	04/08/83
		DE-A-	3202118	28/07/83
EP-A- 0002742	11/07/79	GB-A,B	2010836	04/07/79
		NL-A-	7812312	26/06/79
		DE-A-	2854354	05/07/79
		FR-A,B	2422620	09/11/79
		FR-A-	2422677	09/11/79
		JP-A-	54109955	29/08/79
		AU-A-	4286178	28/06/79
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		AU-A-	1435683	17/11/83

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 84/00280

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [8]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3]: C 07 C 69/78; 63/66; 103/75; C 07 D 335/06; 311/58; 405/06; 409/06; 213/79; 233/36; 239/28; 241/24; A 61 K 31/00

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC[3]	C 07 C 69/00; 63/00; 103/00; C 07 D 335/00; 311/00; A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	EP, A, 0084667 (BASF) 3 August 1983 see the whole document, in particular examples 1-23 --	1-4,9-48
A	EP, A, 0002742 (HOFFMANN LA ROCHE) 11 July 1979 see the whole document, in particular examples 1-20,33-35 (cited in the application) --	1-4,9-48
P	GB, A, 2119801 (HOFFMANN LA ROCHE) 23 November 1983 see the whole document ------	1-4,7,8,9-48

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [9]	Date of Mailing of this International Search Report [9]
18th June 1984	11 JUIL. 1984
International Searching Authority [1]	**Signature of Authorized Officer [10]**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg